NOVARTIS

Global Clinical Development - General Medicine

ZOL 446 / zoledronic acid

Clinical Trial Protocol CZOL446H2337 / NCT00799266

A multicenter, randomized, double-blind, placebo controlled efficacy and safety trial of intravenous zoledronic acid twice yearly compared to placebo in osteoporotic children treated with glucocorticoids

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List of abbreviations

AE	Adverse Event
AKI	Acute Kidney Injury
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMC	Bone Mineral Content
BMD	Bone Mineral Density
BSAP	Bone Specific Alkaline Phosphatase
CDS	Core Data Sheet (for marketed drugs)
CRF	Case Report/Record Form (electronic)
CRO	Contract Research Organization
DXA	Dual Energy X-ray Absorptiometry
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of Study
FPS-R	Faces Pain Scale - revised
FT4	Free Thyroxine
GC	Glucocorticoids
GCP	Good Clinical Practice
GIO	Glucocorticoid-induced osteoporosis
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IL-6	Interleukin 6
i.v.	intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
LFT	Liver Function Test
LS	Lumbar Spine
MedDRA	Medical Dictionary for Regulatory Activities
NTX	Cross-linked N-telopeptide
OC/RDC	Oracle Clinical/Remote Data Capture
OI	Osteogenesis Imperfecta
ONJ	Osteonecrosis of the Jaw
PMO	Postmenopausal Osteoporosis
RBC	Red Blood Cell
RDA	Recommended Daily Allowance
SAE	Serious Adverse Event
SLE	Systemic Lupus Erythematosus

SUSAR	Suspected Unexpected Serious Adverse Reactions
TRAP-5b	Tartrate-resistant Acid Phosphatase Isoform 5b
TNF	Tumor Necrosis Factor
TD	Study Treatment Discontinuation
UK	United Kingdom
WBC	White Blood Cell
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Assessment	A procedure used to generate data required by the study
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Medication pack number	A unique identifier on the label of each investigational drug package
Patient ID	A unique number assigned to each patient upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Amendment 5

Amendment rationale

- The main purpose of this amendment is to address Health Authority requests to provide a Risk Benefit statement (Section 3.6) previously included under introduction and purpose (Section 3.6), and allow more countries to apply the contraceptive wording originally provided for UK sites only.
- In addition, the DMC concerns regarding potential for transient symptomatic hypocalcemia after first infusion are addressed by adding additional calcium supplementation at the recommended daily allowance (RDA) for age in Table 5-1 for up to 10 days around time of infusion (in line with Institutional clinical practice guidelines).
- Table 5-1 has been revised in line with the current minimum RDAs for vitamin D and calcium from the Institute of Medicine.
- This amendment includes clarification of the list of eligible medical conditions other than chronic rheumatologic conditions or inflammatory bowel disease or Duchenne muscular dystrophy (DMD) already specified previously. These additional conditions are listed in Appendix 7 and the eligibility criteria have been revised to address these as follows:
  - Due to the inclusion of some of these additional medical conditions, the exclusion criterion of renal impairment previously defined as an estimated glomerular filtration rate (GFR) < 35 mL/min/1.73 m^2 at screening has been increased to normal renal function defined as < 60 mL/min/1.73 m^2 based on the Schwartz formula at screening. In addition 'serious renal disease' in DMD has been removed as this is included under the GFR exclusion.
  - The exclusion criterion 'symptomatic cardiac abnormality' in DMD has been redefined as follows because other conditions or concomitant medications, including glucocorticoids can contribute to cardiac disease: Uncontrolled symptoms of cardiac failure or arrhythmia.
  - Serum 25-hydroxy vitamin D concentrations have been revised to the currently accepted definition of normal i.e. < 20 ng/mL or < 50 nmol/L at screening.
- The blood volume required for the analysis of certain markers of bone markers has been reduced from 8.5 mL to 3 mL.
- Inconsistencies have been corrected within the protocol and across supporting documents especially with respect to Serious Adverse Event reporting from signing informed consent.
- In this 12 month study, visit windows have been removed and replaced with a requirement to perform the visit close to the designated day.
- The latest Novartis protocol template has been used to aid the reader in navigating the protocol and more recent references provided that reflect the increase in knowledge of childhood osteoporosis since the protocol was first proposed.
- The 12 month open label extension study CZOL446H2337E1 has been added for all patients who complete this core study.

These changes are implemented throughout the protocol.

Status of the study as of 15-Oct-2015:

Eighteen (18) patients have been randomized onto this study; the proposed changes will have no impact on the interpretation of the data with the exception of the definition of the evaluable (MITT) population which clarifies that patients must all have a baseline DXA (identical to ITT) and at least one post-baseline DXA.

Changes to the protocol

Changes to specific sections of the protocol are shown by track changes in the track changes version of the protocol using ~~strike through red font for deletions~~, and red underlined for insertion.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. The changes herein do not affect the Informed Consent Form to be signed by parent(s) or guardian(s).

Summary of previous amendments

Amendment 4

The main purpose of the amendment (16-Aug-2013) was to extend the study population to include subjects with Glucocorticoid induced osteoporosis (GIO) associated with underlying conditions other than chronic inflammatory disorders.

Relax the LS-BMD Z-score inclusion criteria from -1.0 to -0.5 or worse

Include an assessment of urinary concentration of zoledronic acid at 6 months after dosing.

Amendment 3

The main purpose of Amendment 3 (dated 15-Jul-2010) was to update the original Schwartz Formula to the updated Schwartz formula:

GFR (mL/min/1.73 m2) = k [height (m)/Scr (mg/dl)]

k = Constant

k = 0.41

Amendment 3 also incorporated changes which only apply to the UK sites when they enroll female patients of child bearing potential.

These changes incorporate additional information on theoretical risks to a developing fetus in the Pregnancy section and an additional supervised urine pregnancy test at week 12.

Amendment 2

The main purpose of Amendment 2 (dated 23-Sep-2008) was to allow patients to receive their first study drug infusion (Visit 2) in the out-patient setting at the clinical discretion of the study investigators. In addition, clarification was provided for the definition of “Vitamin D and calcium supplementation” and “low trauma fracture”.

Amendment 1

The main purpose of Amendment 1 (dated 17-Jul-2008) was to clarify and amend the osteoporosis inclusion criteria to include one or more [redacted] lower extremity long bone fractures and/or two or more [redacted] upper extremity long bone fractures. The following items were also amended to refine the protocol and further ensure patient safety: measuring bone-age at screening and month 12; collecting pain assessment by the Faces Pain Scale-Revised (FPS-R) at Baseline, months 3, 6, 9 and 12; [redacted]

Protocol summary

Protocol number	CZOL446H2337
Title	A multicenter, randomized, double-blind, placebo controlled efficacy and safety trial of intravenous (i.v.) zoledronic acid twice yearly compared to placebo in osteoporotic children treated with glucocorticoids
Brief title	A research study of zoledronic acid in children and adolescents with osteoporosis
Sponsor and Clinical Phase	Novartis Phase IIIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To evaluate the efficacy and safety of zoledronic acid plus vitamin D and calcium compared to placebo plus vitamin D and calcium in osteoporotic children treated with glucocorticoids
Primary Objective(s)	To demonstrate that 0.05 mg/kg (max 5 mg) zoledronic acid administered every 6 months is superior to placebo for the change in lumbar spine (LS) bone mineral density (BMD) Z-score at Month 12 relative to baseline.
Secondary Objectives	1: To evaluate between-treatment differences for the change in LSBMD Z-score at Month 6 relative to baseline 2: To evaluate between-treatment differences for the change from baseline in lumbar spine and total body bone mineral content (BMC) at 6 and 12 months 3: To evaluate between-treatment differences for the change in serum P1NP, NTX, BSAP & TRAP-5b at Months 6 and 12 relative to baseline 4: To evaluate between-treatment differences for the proportion of patients with new vertebral fractures at Month 12 relative to baseline 5: To evaluate the between-treatment differences for change in vertebral morphometry at Month 12 relative to baseline 6: To evaluate the between-treatment differences for change in pain using the Faces Pain Scale-Revised (FPS-R) at Months 3, 6, 9 and 12 relative to baseline. 7: To evaluate the between-treatment differences for change in 2nd metacarpal cortical width at Month 12 relative to baseline. 8: To measure urinary concentration of zoledronic acid at Month 12 9: To demonstrate that zoledronic acid is safe for the treatment of osteoporotic children treated with glucocorticoids for chronic inflammatory conditions through the monitoring of relevant clinical and laboratory safety parameters.
Study design	This will be an international, multi-center, randomized, double-blind, placebo controlled efficacy and safety study recruiting patients receiving glucocorticoid therapy of any duration within the 12 months preceding screening
Population	The trial population will consist of male and female patients aged 5 to 17 years with confirmed diagnosis of non-malignant conditions requiring treatment with systemic glucocorticoids. Approximately 92 patients will be randomized in a multicenter setting, to

	yield at least 82 patients evaluable for the primary endpoint.
Key Inclusion criteria	• Written informed consent before any study related procedure • Children, male or female, between 5 and 17 years of age at Visit 1 of the study • Confirmed diagnosis of a chronic inflammatory condition including rheumatic conditions or inflammatory bowel disease (IBD) non-malignant conditions requiring treatment with systemic glucocorticoids (including but not limited to rheumatic conditions, Inflammatory Bowel Disease, Duchenne muscular dystrophy), requiring treatment with systemic glucocorticoids (i.v. or oral) within the 12 months preceding enrollment in the study (any duration) • LS-BMD Z-score of -0.5 or worse confirmed by the central imaging vendor • Evidence of at least 1 vertebral compression fracture (at least Genant Grade 1 vertebral compression or radiographic signs of vertebral compression) confirmed by central reading OR At least one lower OR 2 upper extremity long-bone, low-trauma, fracture which occurred sometime within the 2 years or preceding enrollment in the study, confirmed by central reading or radiological report. (Low trauma fracture is defined as falling from standing height or less).
Key Exclusion criteria	• History of primary bone disease (osteogenesis imperfecta, idiopathic juvenile osteoporosis, rickets/osteomalacia). • Prior use of bisphosphonates or sodium fluoride (doses for osteoporosis not for dental hygiene). • Any medical condition that might interfere with the evaluation of LS-BMD, such as severe scoliosis or spinal fusion. • Hypocalcemia and hypophosphatemia: any value (age-matched) below the normal range at screening • Vitamin D deficiency (serum 25-hydroxy vitamin D concentrations of < 20 ng/mL or < 50 nmol/L) at screening • Renal impairment defined as an estimated glomerular filtration rate (GFR) < 60 mL/min/1.73 m2 at screening based on the Schwartz formula; a serum creatinine increase between Visit 1 and Visit 2 greater than 0.5 mg/dL (44.2 µmol/L) • Female patients of child bearing potential are eligible only if they are not pregnant/non-lactating. Females of child bearing potential must be practicing a medically acceptable form of birth control for greater than 2 months prior to screening visit and consent to pregnancy tests during the study.
Study treatment	i.v. zoledronic acid (ZOL446 or placebo) 5.0 mg/100 mL solution, supplied in a ready-to-infuse plastic bottle
Efficacy assessments	Primary Efficacy Assessment: LS-BMD Z-score measurement at screening and Month 12. Secondary Efficacy Assessments: • LS-BMD Z-score at Month 6. • LS and total body BMC at 6 and 12 months. • Serum P1NP and BSAP at Months 6 and 12. • Serum NTx and TRAP5b at Months 6 and 12. • Number of patients with new vertebral fractures at Month 12 and baseline, based on a lateral thoracolumbar spine X-ray (including

	radiographic signs of fractures and Genant classification fractures). • Vertebral morphometry based on a lateral thoracolumbar spine X-ray, at Month 12 and baseline. • FPS-R at Months 3 6, 9 and 12. • 2nd metacarpal cortical width at Month 12 and baseline.
Key safety assessments	Adverse event monitoring, Physical examinations, Monitoring of laboratory markers in blood and urine; bone safety monitoring and bone age.
Other assessments	[redacted]
Data analysis	The primary efficacy variable, the change in LS-BMD Z-score at Month 12 relative to baseline, will be analyzed using an analysis of covariance model with treatment, pooled centers, underlying condition, and baseline LS-BMD Z-score as explanatory. If conditions of normality are not satisfied, appropriate non-parametric methods will be utilized. Other secondary BMD-related endpoints will be evaluated similarly. The analysis of changes in serum BSAP, P1NP, NTX& TRAP-5b will be performed based on the relative change from baseline computed as the loge ratio of the post-baseline measurement divided by the baseline measurement at each time point. Between-treatment differences will be evaluated using an ANCOVA model with treatment, pooled centers, underlying condition treated with glucocorticoids, and [redacted] Other variables measured will be presented descriptively in tabular or graphical format, as appropriate by treatment group.
Key words	Osteoporosis, children and adolescents, zoledronic acid, chronic inflammation, Duchenne muscular dystrophy, glucocorticoids

1 Introduction

1.1 Background

Osteoporosis in children is a very different disease to osteoporosis in adults. Children have not attained peak bone mass, and sufficient data correlating bone density with fractures are not available. The role of lumbar spine bone mineral density (LS-BMD) in the risk of fracture has been evaluated in some childhood illnesses, particularly osteogenesis imperfecta (primary osteoporosis). Although the diagnosis of osteoporosis in adults is based on BMD, Sbrocchi 2011 reported a child with glucocorticoid responsive nephrotic syndrome and fragility fracture; bone biopsy revealed signs of osteoporosis with marked thinning of the cortices and decreased trabecular bone volume, suggesting that DXA-based, LS-BMD should not be relied upon exclusively for assessing bone health in children, and that a LS-BMD Z-score of -0.5 is sufficient. Further, the International Society for Clinical Densitometry (ISCD) now defines pediatric osteoporosis as the finding of one or more low impact vertebral compression fractures (Genant Grade 1 or more) in the absence of a change in BMD (Bishop et al 2014).

Patients receiving high doses of glucocorticoids are at increased risk of significant bone loss and fractures; glucocorticoid-induced osteoporosis (GIO) is now recognized as one of the most important reasons for secondary osteoporosis in adults as well as children. Prior glucocorticoid use confers a substantial increase in fracture risk in adults, and this risk is largely independent of BMD or a prior fragility fracture (Kanis et al 2004). Studies in adults suggest that glucocorticoid treatment for 3 months is sufficient to increase fracture risk, and similar data have been collected in children and adolescents where almost one-half of the patients with fractures were asymptomatic (Leblanc et al 2015). The earliest observation of vertebral fractures in children with rheumatic disorders is 4 months after starting systemic glucocorticoids (Rodd et al 2012).

The etiology of secondary osteoporosis in children with inflammatory disorders is multifactorial and varies with the particular disease. Overlapping risk factors seen in chronic inflammatory conditions include poor nutrition and malabsorption of both calcium and fat-soluble vitamins. Direct detrimental effects on bone due to high circulating levels of pro-inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha have been reported. The treatment of inflammatory bowel disease (IBD), juvenile rheumatoid arthritis (JRA), systemic lupus erythematosus (SLE), Duchenne muscular dystrophy (DMD), and nephrotic syndrome includes glucocorticoid therapy which further worsens bone mineral status.

While there is no primary bone involvement in DMD, the reduced mechanical loading and poor ambulation lead to osteoporosis, which is further compounded by the side effects of chronic glucocorticoid therapy. Osteoporosis is most profound in the lower extremities of boys with DMD and begins to develop early while still ambulatory (Larson 2000). Other examples of diseases of children treated with intermittent high doses of glucocorticoids where osteoporosis is also a risk include asthma, myasthenia gravis and Becker's dystrophy, and etc. (see Appendix 7).

There is no established treatment for secondary osteoporosis in children, although treatment for adult osteoporosis including GIO is currently well established for bisphosphonates. Placebo controlled trials using bisphosphonates such as risedronate and alendronate have been shown to increase BMD and reduce the risk of vertebral fractures in patients initiating glucocorticoids or receiving such a treatment for a longer period of time. In adults, regulatory approval for treatment and prevention of osteoporosis has been granted for bisphosphonates. Although bisphosphonates have been used experimentally in the treatment of specific pediatric metabolic bone disease, only one, neridronate is currently approved in Italy for osteogenesis imperfecta (OI). Pamidronate is provided as an example of bisphosphonates for consideration in the management of DMD boys with 'bone demineralization and increased fracture risk' (Bushby et al 2009).

Zoledronic acid

Zoledronic acid (ZOL) is representative of a third generation bisphosphonate and is the most potent bisphosphonate marketed. In a variety of assays of bone metabolism, ZOL has demonstrated inhibition of bone resorption in vitro at concentrations of 0.3-30 nM and in vivo at doses of 0.3-30µg/kg without exerting any untoward effects on either bone formation or mineralization. A large difference exists between various bisphosphonates in terms of potency and effects on mineralization. There is an inverse relationship between potency and mineralization defects. These mineralization defects have occurred in patients treated with the upper therapeutic dose range of etidronate. In animal models, zoledronic acid has demonstrated extremely high potency in terms of antiresorptive effect without adverse effects on mineralization even at high doses; hence there appears to be a large therapeutic window between the desired inhibition of resorption and unwanted inhibition of mineralization in these models [see Investigator' Brochure (IB)].

ZOL is marketed as Aclasta® outside of the US and for Paget's disease of bone and PMO as Reclast® within the US. As Aclasta, ZOL is approved as a single infusion for the treatment of Paget's disease of bone and as once annual dosing for the treatment of postmenopausal osteoporosis (PMO), treatment of osteoporosis in men, prevention and treatment of glucocorticoid-induced osteoporosis (GIO), prevention of postmenopausal osteoporosis (PMO) and prevention of clinical fractures after hip fracture in men and women. Moreover, it is approved for the prevention of skeletal-related events (pathological fractures, spinal compression, radiation or surgery to bone) or tumor-induced treatment of hypercalcemia of malignancy as Zometa® using a 10-fold higher dose on a yearly basis (4mg once monthly). Aclasta/Reclast is currently under review for the additional indications of treatment and prevention of GIO and the treatment of low bone mass in men with osteoporosis. Further information can be found in the current version of the IB.

A 2007 Cochrane Review (Ward et al 2007) of bisphosphonate therapy for children and adolescents with secondary osteoporosis concluded that though there was not enough information in the studies included within the review to assess if bisphosphonates would make a difference to children's bone mineral content (BMC), and that further use of bisphosphonates in the context of pediatric trials was justified.

1.2 Purpose

Zoledronic acid is marketed in many countries for adults with weak bones, including osteoporosis associated with the use of glucocorticoids (or steroids). The purpose of this study is to determine the bone strengthening effect of ZOL compared to placebo in osteoporotic children treated with glucocorticoids for Duchenne muscular dystrophy or chronic inflammatory conditions including rheumatic conditions and inflammatory bowel disease. In addition, the safety of zoledronic acid will be assessed. Patients who complete this 12 month study will be offered participation in a 12 month extension study where all patients will receive zoledronic acid.

2 Study objectives and endpoints

2.1 Primary objective(s)

The primary objective of the study is to demonstrate that 0.05 mg/kg (max 5 mg) zoledronic acid administered every 6 months is superior to placebo for the change in lumbar spine (LS) bone mineral density (BMD) Z-score at Month 12 relative to baseline.

2.2 Secondary objective(s)

1. To evaluate between-treatment differences for the change in LS-BMD Z-score at Month 6 relative to baseline.
2. To evaluate between-treatment differences for the change in LS and total body BMC at 6 and 12 months.
3. To evaluate between-treatment differences for the change in serum P1NP, BSAP, NTX, and TRAP-5b at Month 6 and Month 12 relative to baseline.
4. To evaluate between-treatment differences for the proportion of patients with new vertebral fractures at Month 12 relative to baseline.
5. To evaluate the between-treatment differences for change in vertebral morphometry at Month 12 relative to baseline.
6. To evaluate the between-treatment differences for change in pain using the Faces Pain Scale-Revised (FPS-R) at Months 3, 6, 9 and 12 relative to baseline.
7. To evaluate the between-treatment differences for change in 2nd metacarpal cortical width at Month 12 relative to baseline.
8. To measure urinary concentration of zoledronic acid at Month 12.
9. The safety objective is to demonstrate that zoledronic acid is safe for the treatment of osteoporotic children treated with glucocorticoids through the monitoring of relevant clinical and laboratory safety parameters.

2.4 Objectives and related endpoints

Table 2-1 Objectives and related endpoints- Objectives

OBJECTIVE	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure	Stat Analysis Section
Primary		
To demonstrate that zoledronic acid 0.05 mg/kg (max 5 mg) administered every 6 months is superior to placebo for the change in lumbar spine (LS) bone mineral density (BMD) Z-score at Month 12 relative to baseline.	*Title*: Change in LS-BMD Z-score *Description*: LS-BMD Z-score will be determined by the central imaging vendor before first treatment and at Month 12. The methods to be used to measure LS-BMD are described in the respective DXA Manuals provided by central imaging vendor *Time Frame* : baseline, Month 12	Section 9.4.1
Secondary		
To evaluate between-treatment differences for the change in LS-BMD Z-score at Month 6 relative to baseline.	*Title*: Change in LS-BMD Z-score *Description*: LS-BMD will be determined by the central imaging vendor before first treatment and at Month 6. The methods to be used to measure LS-BMD are described in the respective DXA Manuals *Time frame*: baseline and 6 months	Section 9.5.1.1
To evaluate between-treatment differences for the change in LS and total body BMC at 6 and 12 months.	*Title*: Change in LS and total body BMC *Description*: LS and total body BMC will all be determined by the central imaging vendor before first treatment and at Months 6 and 12. The methods to be used to measure BMC are described in the respective DXA Manuals *Time frame*: baseline, 6 and 12 months	Section 9.5.1.2
To evaluate between-treatment differences for the change in serum P1NP, BSAP, NTX, and TRAP-5b at Month 6 and Month 12 relative	*Title*: relative change in bone markers *Description*: Serum P1NP, BSAP, NTX, and TRAP-5b will be collected before first treatment (baseline) and at Months 6 and 12 according to the instructions provided in the Laboratory	Section 9.5.1.3

OBJECTIVE	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure	Stat Analysis Section
to baseline.	manual. The samples will be analyzed in batches at the laboratory *Time frame*: baseline, 6 and 12 months	
To evaluate between-treatment differences for the proportion of patients with new vertebral fractures at Month 12 relative to baseline.	*Title*: Incidence of new vertebral fractures *Unit of measure*: number and percentage of new vertebral fractures *Description*: See Section 6.4.1 *Time frame*: baseline, and 12 months	Section 9.5.1.4
To evaluate the between-treatment differences for change in vertebral morphometry at Month 12 relative to baseline.	*Title*: Change in vertebral morphometry *Description*: Quantitative morphometry will be performed by a central reader (see Section 6.4.1) *Time frame*: baseline, and 12 months	Section 9.5.1.5
To evaluate the between-treatment differences for change in pain using the Faces Pain Scale-Revised (FPS-R) at Months 3, 6, 9 and 12 relative to baseline.	*Title*: Change in pain scale *Description*: Children will select the face that best fits their pain (Appendix 4) *Time frame*: baseline, 3, 6, 9 and 12 months	Section 9.5.1.7
To evaluate the between-treatment differences for change in 2nd metacarpal cortical width at Month 12 relative to baseline.	*Title*: Change in metacarpal cortical width *Description*: The X-ray Manual provides instructions on the technique. Skeletal bone age will be determined as described in the Imaging Charter *Time frame*: baseline and 12 months	Section 9.5.1.6
To measure urinary concentration of zoledronic acid at Month 12.	*Title*: Pharmacokinetics *Unit of measure*: ng/mL *Description*: urine will be collected overnight or for at least 4 waking hours from all patients able to provide specimens *Time frame*: 12 months	Section 9.5.3
The safety objective is to demonstrate that zoledronic acid is safe for the treatment of osteoporotic children treated with glucocorticoids through the monitoring of relevant clinical and laboratory safety parameters	*Title*: Safety: adverse events, laboratory evaluations and vital signs *Description*: adverse events will be collected from the first infusion (Visit 2), blood and urine samples, including renal monitoring will be collected (See Section 6.5). Also bone safety (change in LS-BMD) is monitored at months 6 and 12. *Time frame*: baseline through 12 months	Section 9.5.2

3 Investigational plan

3.1 Study design

This will be an international, multicenter, randomized, double-blind, placebo controlled efficacy and safety study recruiting osteoporotic children and adolescents receiving glucocorticoid therapy within the 12 months preceding screening who manifest a LS-BMD Z-score of -0.5 or worse plus evidence of low impact/fragility fracture.

At the baseline visit (Visit 2), patients whose eligibility is confirmed will be randomized to one of two treatment groups. Patients may be hospitalized at the discretion of the investigator for observation following the first study drug infusion. Ionized calcium will be assessed before the first study drug infusion only. Patients will receive the second study drug infusion at the Month 6 visit. Safety and efficacy will be assessed at 6 and 12 months, with additional telephone visits to assess adverse events [redacted] and concomitant medication at 3 and 9 months. Renal safety utilizing the Schwartz calculation for GFR will be assessed at screening, and 10 days after the i.v. infusion of study drug 6 and 12 months.

3.2 Rationale for study design

The patient population will be described in more detail in the Section 4 below.

A placebo control design is being utilized because currently there is no approved therapy to treat children with secondary osteoporosis and there is no clinically accepted off-label gold standard of therapy for this pediatric patient population. In adults, an improvement in BMD can often be achieved with oral administration of calcium and vitamin D (ACR Task Force 1996). All children enrolled in this study will be provided with conservative intervention to ensure adequate dietary intake of calcium and vitamin D, regardless of their treatment assignment (diet with or without supplements).

3.3 Rationale for dose/regimen, route of administration and duration of treatment

Zoledronic acid dose selection for Study CZOL446H2337 is based on several sources of information, including safety and efficacy data from completed Novartis clinical trials in adults with postmenopausal osteoporosis, pediatric patients with severe OI, long-term safety in pediatric patients with OI, and a PK study in pediatric patients with severe OI. Published data is available from trials in patients with postmenopausal osteoporosis (Reid 2002; Black 2007). Adults with benign disease (Paget's and PMO) have received ZOL safely up to 5 mg i.v. by slow injection (over 15 minutes) over various dosing frequencies. Cancer patients have received between 4 and 8 mg i.v. monthly, in long-term studies (> 1 year). In the Novartis ZOL pediatric studies to date, the dose schedule was an infusion of 0.05 mg/kg (max 4 mg) administered quarterly. This dose was extrapolated from a comparison with a pamidronate infusion in patients with tumor-induced hypercalcemia that showed that 4 mg ZOL was more effective than 90 mg pamidronate. The 4 mg dose of ZOL represents an approximate adult dose of ZOL of 0.07 mg/kg or a dose of pamidronate of 1.5 mg/kg for a 60 kg adult. Pamidronate 1.5 or 3.0 mg/kg administered every 6 months was the dose range and interval used in the long-term pamidronate OI study (Glorieux et al 1998). However, in this trial, the

pamidronate dosing interval was shortened to a 4-month dosing regimen to improve the response in bone markers of disease activity, monitored each month.

Study CZOL446H2202 (see IB) is the largest Novartis-sponsored trial in pediatric patients with metabolic bone disease. This 12-month study compared the efficacy and safety of i.v. zoledronic acid 0.05 mg/kg administered quarterly to i.v. pamidronate 1.0 mg/kg on each of 3 successive days administered quarterly in 155 patients with severe OI. The results showed that ZOL was superior to pamidronate in increasing LS-BMD at Month 12 and in reducing markers of bone turnover, both formation and resorption. Additionally, clinical fracture reduction within treatment was significant overall, and regardless of OI type. The overall incidence rate of adverse events was similar between the two treatment groups. There was no evidence of a long-term effect on renal function following the administration of ZOL in this patient population. The pharmacokinetics of a single infusion of ZOL 0.05 mg/kg, in children aged 3-8 years and 9-17 years, were similar to those observed in adult oncology patients at approximately the same mg/kg dose. Plasma concentrations in the pediatric patients were generally at or below the median concentrations in adults, which may be an advantage in consideration of drug safety and tolerability in children.

In a second trial with OI patients (see IB for study CZOL446H2202E1), the 12-month extension study, long-term safety was assessed in 103 patients receiving 0.05 mg/kg zoledronic acid either as an annual infusion or twice a year (6 months apart). In this study, median increases in LSBMD were approximately 1.3% higher in patients who received the twice yearly dosing of zoledronic acid. Though these data from the extension study should be interpreted with caution as the sample sizes are too small to make definitive conclusions, it is established that there is an effect of puberty on bone degradation, with children demonstrating high bone resorption relative to adults.

Therefore, the zoledronic acid dose and interval selected for this protocol, 0.05 mg/kg as two i.v. infusions at a 6 month interval, is expected to provide superior efficacy (as measured by change in LS-BMD Z-score) compared to placebo in pediatric patients with osteoporosis. The maximum allowable zoledronic acid dose of 5 mg (regardless of patient weight), does not exceed the doses already used in adults and is well within the maximum zoledronic acid dose tested in Phase I Novartis Oncology trials: zoledronic acid 16 mg by slow i.v. infusion. In this study in children with osteoporosis, zoledronic acid will be administered as an i.v. infusion over at least 30 minutes.

3.4 Rationale for choice of comparator

A placebo control has been selected because there is no standard treatment for this condition and although many pediatricians use bisphosphonates to treat fractures in children, the efficacy and safety of bisphosphonate therapy still needs to be determined in a population with secondary osteoporosis.

3.5 Purpose and timing of interim analyses/design adaptations

It is not intended that an interim analysis will be conducted for this study.

3.6 Risks and benefits

Benefit

The potential benefit of zoledronic acid in children at risk of osteoporosis due to underlying disease or intermittent high dose glucocorticoids is outlined below and in the IB.

There is evidence that bisphosphonates have anti-apoptotic effects on osteoblasts and osteocytes which may lead to increased trabecular thickness and thus, may partly explain why bisphosphonates produce a greater reduction in fracture risk than that expected from BMD gains alone (Plotkin 1999). Furthermore, BMD is greatly influenced by sex steroids, and puberty can be delayed in the presence of GC which can also result in short stature which may be offset by the use of bisphosphonates (Glorieux et al 1998).

The most commonly studied bisphosphonate in children has been i.v. pamidronate in the treatment of a primary juvenile osteoporosis, osteogenesis imperfecta (OI). The typical treatment protocol reported in OI is administration of pamidronate on three consecutive days in hospital (Glorieux et al 1998). There is some variation of dosing frequency (typically every 1 to 4 months, depending upon the age of the patient, with younger patients receiving more frequent infusions). Treatment requiring three consecutive days of intravenous therapy every several months can cause a significant burden of both time and cost. The efficacy of cyclic single-day intravenous pamidronate infusions in a heterogeneous group of patients between 6 to 21 years of age was studied and demonstrated similar improvements in bone density and in fracture rate as reported with 3-day infusions in patients with OI (Steelman 2003).

A direct comparison of 2-day pamidronate (PAM) to a 2-day infusion of ZOL has been published in 23 children with OI (Barros et al 2012). Twelve months after treatment, the PAM and ZOL groups average LS-BMD increased by 51.8 % ($p = 0.053$) and 67.6 % ($p = 0.003$), respectively. LS-BMD Z-score for the ZOL group at the end of treatment was higher compared with the PAM group but only a borderline significance ($p = 0.053$). Only mild side effects were reported in both groups and the authors concluded that ZOL was not different from PAM in efficacy and safety in this group of children. More recently, a retrospective study reviewed treatment with PAM and ZOL and followed up the children for up to 2 years (Bowden et al 2015). The authors reported that i.v. bisphosphonate therapy significantly increased BMD and reduced fracture rate during the treatment with a beneficial effect in BMD maintained for 2 years after discontinuation of therapy. A second retrospective study reviewed PAM administered in cycles of 1.5 mg/kg per day over 2 days every 3 months and ZOL as a single dose of 0.05 mg/kg every 6 months to patients aged at least 5 years with type I or IV OI (Saraff et al 2015). Twenty children were identified in each group; LS-BMD Z-scores increased significantly in both groups over 12 months ($p<0.001$) with no significant differences shown between PAM and ZOL. Another study has been conducted by the sponsor to evaluate the efficacy and safety of ZOL as compared to pamidronate in the treatment of children with severe OI (Study CZOL446H2202 described in IB). The ZOL treated group, had a mean 42.7% increase from baseline in LS-BMD at Month 12 compared with a mean increase of 34.7% in the pamidronate treated group. These changes were consistent with pediatric OI literature which has reported an annualized increase in BMD of 41.9% with cyclical pamidronate (Glorieux et al 1998). The deviation from normal, as measured by the LS-BMD Z-score, at both 6 and 12 months showed an improvement with ZOL. Importantly,

both treatments reduced the occurrence of clinical fractures per patient significantly ($p<0.0001$) following 12 months of treatment, although the proportion of patients who had clinical fractures in the 12 months of study treatment was similar in the two groups (ZOL: 32 patients, 43.2%; pamidronate: 31 patients, 40.8%; HR 1.05, 95% CI 0.64 – 1.72). Of note, there was a higher risk of clinical fracture in the type I patients treated with ZOL compared to pamidronate (HR 2.12, 95% CI 0.96 – 4.69), and a lower risk of clinical fracture in the type III and IV patients treated with zoledronic acid compared to those patients treated with pamidronate (HR 0.59, 95% CI 0.29 – 1.19).

The evidence of bisphosphonate therapy in children and adolescents with secondary osteoporosis has been reviewed (Ward et al 2007). More recent retrospective studies and reviews on zoledronic acid in children with osteoporosis have been published which report benefits on BMD, bone pain and fractures (Baroncelli and Bertollini 2014, Boyce et al 2014, Brown and Zacharin 2009) and authors agree that prospective randomized controlled trials are still needed to evaluate the benefit risk of bisphosphonates. An increasing number of pediatric metabolic bone experts now reserve bisphosphonate therapy for the management of low bone mass in children and adolescents who have symptoms of a fragility fracture (Boyce and Gafni 2011), and there is one recent publication on the prophylactic use of bisphosphonates in the management of boys with Duchenne muscular dystrophy (DMD) who are receiving long-term glucocorticoids (Sarkozy et al 2014).

Risks

Known risks of zoledronic acid

Since this protocol was first written in 2008, there have been more publications on the potential use of bisphosphonates in children with kidney diseases including nephrotic syndrome (Gruppen et al 2013, Sbrocchi et al 2011).

ZOL is concentrated and excreted via the kidney and, like other bisphosphonates, has the potential to produce renal injury. Thus, care should be taken when administering the compound to patients with renal insufficiency. Although case reports have been published in adult medicine regarding the nephrotoxicity of ZOL with an incidence of acute kidney injury (AKI) between 9% and 13%, bisphosphonate-induced, AKI in children remains undocumented (Patzer 2008).

- In this protocol, patients are excluded if they have an estimated GFR < 60 mL/min/1.73 m^2 or a rising serum creatinine increase greater than 0.5 mg/dL (44.2 µmol/L) between Visit 1 and Visit 2. Patients who have nephrotic syndrome with osteoporosis, who do not meet these exclusion criteria, have been stable for 3 months prior to enrollment, and meet the remaining eligibility criteria can be considered for this study.

Post-infusion acute phase reactions are more common after the first infusion and can include pyrexia, muscle and joint pain.

- To reduce the risk of these reactions, children will be instructed to eat and drink as usual, NSAIDs or acetaminophen (paracetamol) will be prescribed and an anti-emetic may be provided to reduce the risk of symptomatic hypocalcemia if the child develops nausea or starts to vomit. Further calcium supplements will be provided for up to 10 days at the time

of infusion and parent/guardian instructions provided on the signs to watch for as well as an emergency number, if needed.

Hypersensitivity reactions including anaphylactic reaction, anaphylactic shock, angioedema, bronchospasm and urticaria are listed in the IB. Therefore, children with a previous known hypersensitivity are excluded. Should a child develop a hypersensitivity reaction, it must be reported as an adverse event.

A rare risk in patients who receive bisphosphonates is osteonecrosis of the jaw (ONJ). This condition has been reported primarily in cancer patients whose complex treatment regimens include higher doses and frequencies of bisphosphonates, typically administered with other treatments such as radiation, chemotherapy and glucocorticoids. To date and to the best of our knowledge, ONJ has not been reported in the literature in children or adolescents who have received bisphosphonates. Based on available evidence, a causal relationship between ONJ and bisphosphonates, including ZOL, has not been established.

- In this study a lower dose and short duration of zoledronic acid is used than has been reported in cases of ONJ in adults, and all children will have an examination of their oral cavity during the study and referred to a dentist if necessary.

Potential risks of zoledronic acid in a pediatric population

Based on the results from animal studies showing inhibition of bone calcification by first generation bisphosphonates (Mashiba 2001), there are theoretical concerns about negative effects on growth in children. In growing children, each bisphosphonate treatment cycle leads to the accumulation of a thin band of mineralized tissue at the interface between growth plate and metaphysis which is evident as a metaphyseal line on the radiograph (Land et al 2006a). These lines represent persistent calcified cartilage in the horizontal trabeculae which later remodels into secondary bone. This interface between weaker bone and stronger bisphosphonate-treated bone could represent a site for potential fracture. However, in clinical trials with i.v. bisphosphonates, linear growth in children and adolescents has not been observed to be negatively impacted with no observed increase in fracture. To the contrary, cyclical i.v. treatment with pamidronate has been shown to be beneficial in children with severe forms of OI (Glorieux et al 1998).

- To investigate this potential risk, a placebo control is used for comparison; all patients will have DXA examination at 6 and 12 months and in the event of clinical worsening or diagnosis of new fracture, an X-ray will be performed.

Another concern in children is effects on the reproductive organs. The animal reproduction studies of zoledronic acid are described in the Investigator's Brochure. Teratogenicity was observed in the rat, but not the rabbit when treatment during the perinatal period resulted in delayed parturition likely resulting from the calcium lowering effect of the compound outside of bone, which negatively affects uterine contraction. There were no effects reported in males.

- Consequently this protocol requires contraception in all girls who are pubertal and may become pregnant and in some countries additional pregnancy checks will be made.

There are potential concerns regarding the i.v. infusion in children. Apart from the potential risks at the infusion site of pain, infection, phlebitis, hematoma and extravasation, the infusion may also cause fluid overload if the rate is too high and this can result in hypertension, heart

failure or pulmonary edema. Additional risks of the infusion can include electrolyte imbalance and embolism.

- The infusion is administered in a hospital or clinic by staff experienced in administering i.v. infusions to children. The infusion line is flushed with saline before and after administration and the infusion given over at least 30-minutes e.g. in a 25 kg child, 100 mL may be administered over one hour at a rate of 5 mL/minute.

Protocol procedures: blood draws and radiology

The number of blood draws and frequency of hospital visits in this protocol is within the usual limit of clinical practice for children with these serious underlying diseases. The radiation exposure is increased over routine clinical practice, but within the limits for children who have suffered a fracture and no greater than the exposure during a transatlantic flight. Repeat blood draws and X-rays/DXA will only be requested when absolutely necessary i.e. safety, baseline or end-of-study visits.

In summary, the risks to the children and adolescents in this trial will be minimized by compliance with the eligibility criteria and study procedures, particularly adequate hydration at the time of the infusion, adherence to a diet rich in calcium and vitamin D, regular renal monitoring and contraception in girls of child bearing potential. A maximum dose of 5 mg zoledronic acid (regardless of patient weight) and a minimum 30 minute infusion time 6-monthly are designed to reduce the risk of possible adverse effects. This dose regimen has been used in children with primary and secondary osteoporosis and has shown a favorable risk-benefit profile.

4 Population

The trial population will consist of male and female patients aged from 5 to 17 years old, with a confirmed diagnosis of non-malignant conditions requiring treatment with systemic glucocorticoids (including but not limited to rheumatologic conditions, inflammatory bowel disease, Duchenne muscular dystrophy, nephrotic syndrome) and who have been treated with systemic glucocorticoids (i.v. or oral) within the 12 months preceding screening; with evidence of at least one vertebral compression fracture, or one or more [redacted] lower extremity long bone fractures, or two or more [redacted] upper extremity long bone fractures, confirmed by central reading. Approximately 92 patients will be randomized from approximately 30 centers in a multicenter setting, to yield at least 82 patients evaluable for the primary endpoint.

4.1 Inclusion criteria

Patients/ eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed. An assent needs to be provided in accordance with ICH and local regulations.
2. Children, male or female, between 5 and 17 years of age.
3. A confirmed diagnosis of non-malignant conditions requiring treatment with systemic glucocorticoids (including but not limited to chronic rheumatologic conditions or,

inflammatory bowel disease or Duchenne muscular dystrophy) requiring treatment with systemic glucocorticoids (i.v. or oral) within 12 months prior to screening.

a. Chronic rheumatologic conditions may include: Juvenile Idiopathic Arthritis (JIA):Systemic onset; JIA: Polyarticular rheumatoid factor positive; JIA: Polyarticular rheumatoid factor negative; JIA: Psoriatic arthritis; JIA: Enthesitis-related arthritis; JIA: Oligoarticular arthritis; JIA: Unclassified; Systemic Lupus Erythematosus (SLE); Juvenile Dermatomyositis; Scleroderma (generalized or localized); Overlap Syndromes (including mixed connective tissue disease); Sjogren's syndrome; Systemic Vasculitis, as defined by the Chapel Hill Consensus Conference on Nomenclature: Giant cell (temporal) arteritis, Takayasu's arteritis, Polyarteritis nodosa, Wegener's granulomatosis, Churg-Strauss syndrome, Microscopic polyangiitis, Essential cryoglobulinemic vasculitis, Cutaneous leukocytoclastic angiitis, Behcet's disease, other vasculitis
b. Inflammatory bowel disease may include: Crohn's disease and Ulcerative Colitis
c. Duchenne muscular dystrophy
d. Nephrotic syndrome who have stable normal renal function for at least 3 months prior to screening
e. Other subtypes of secondary osteoporosis in children taking glucocorticoids, except patients with oncologic conditions (such as lymphoma and leukemia) Appendix 7.

4. Lumbar Spine BMD - Z score of -0.5 or worse confirmed by the central imaging vendor.
5. Evidence of at least 1 vertebral compression fracture of Genant Grade 1 or higher or radiographic signs of vertebral compression fracture seen in X-ray within 1 month of or at screening visit, confirmed by central reading. Radiographic signs of fracture include loss of endplate parallelism, vertebral buckling and endplate interruption.

   OR

   - One or more, low-trauma*, lower extremity long-bone fracture which occurred sometime within the 2 years preceding enrollment in the study, confirmed by radiological report

   OR

   - Two or more, low-trauma*, upper extremity long-bone fractures which occurred sometime within the 2 years preceding enrollment in the study, confirmed by radiological report

*Low trauma fracture is defined as falling from standing height or less.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. History of primary bone disease (osteogenesis imperfecta, idiopathic juvenile osteoporosis, rickets/osteomalacia).
2. Any prior use of bisphosphonates, or high dose sodium fluoride (i.e. dental use is permitted).

3. Any medical condition that might interfere with the evaluation of LS-BMD, such as severe scoliosis or spinal fusion. Patients with less than 3 evaluable vertebrae by DXA evaluation in the region of interest L1-L4, as confirmed by the central imaging laboratory, will not be considered eligible for this study.
4. As per investigator's judgment, patient is anticipated to have bone surgery within subsequent year.
5. Hypocalcemia and hypophosphatemia: any value (age-matched) below the normal range at screening.
6. Serum 25-hydroxy vitamin D concentrations of < 20 ng/mL or < 50 nmol/L at screening.
7. Renal impairment defined as an estimated glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 at screening based on the Schwartz formula at screening
8. A serum creatinine increase between Visit 1 and Visit 2 greater than 0.5 mg/dL (44.2 µmol/L).
9. Uncontrolled symptoms of cardiac failure or arrhythmia.
10. History of hyperparathyroidism or hyperthyroidism within 1 year prior to screening.
11. History of hypothyroidism unless on a stable treatment regimen for > 6 months, with at least one documented normal TSH and FT4 levels during this 6 month period.
12. History of sarcoidosis.
13. Diagnosis of active uveitis (symptomatic or asymptomatic) at the time of enrollment in the study.
14. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes
15. Female patients of child bearing potential are eligible only if they are: (1) not pregnant/ non-lactating; (2) are sexually abstinent or are surgically sterile or (3) if sexually active, must be practicing a medically acceptable form of birth control for greater than 2 months prior to screening visit. Females of child bearing potential who are sexually active must agree to continue to practice their birth control during the trial and at least 1 year after completing the trial and must consent to a pregnancy test prior to every dose administration and at the End of Study (EOS) Visit.

- [For sites and/or regions where additional safeguards are required e.g. UK, Italy, Germany, Sweden & etc.: Female patients of child bearing potential are eligible only if they are not pregnant/non-lactating. Females of child bearing potential must be practicing a medically acceptable form of birth control for greater than 2 months prior to screening visit. At least one and preferably two complementary forms of contraception including a barrier method should be used and be continued throughout the trial and for at least 1 year after completing the trial. They must also consent to a pregnancy test prior to every dose administration and at the EOS Visit. An additional supervised urine pregnancy test will be assessed at Week 12 (See Table 6-1 and Section 6.5.5).]

16. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in-situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Zoledronic acid (or placebo) 5.0 mg/100 mL solution, supplied in a ready-to-infuse plastic bottle.

5.1.2 Additional treatment

Adequate intake of vitamin D and calcium is mandatory for the four weeks prior to randomization and throughout the duration of the study, i.e. 12 months, either through adequate dietary intake or via supplementation, or a combination of both diet and supplementation. Described below are the recommended guidelines for vitamin D and calcium intake. It is the responsibility of the investigator to ensure that each patient receives the adequate recommended daily allowance of vitamin D and calcium (through diet and/or supplementation).

Table 5-1 Recommended minimum daily dietary allowances (Ross 2011)

Age	Vitamin D	Calcium
≥ 5 years to ≤ 8 years	600 IU	1000 mg
≥ 9 years to ≤ 17 years	600 IU	1300 mg

All patients should take at least 600 IU vitamin D daily from Visit 1 until the final Visit through diet and/or supplementation.

Elemental calcium, at least 1000 mg for 5-8 years of age or at least 1300 mg for 9-17 years of age, daily will be taken beginning at Visit 1 and during the total duration of the trial, through diet and/or supplementation. Calcium carbonate is the preferred form of calcium supplementation. If calcium carbonate is not well tolerated, another form of oral calcium would be acceptable.

Any vitamin D and calcium supplements will be recorded on the Concomitant medications/Significant non-drug therapies (e)CRF.

In addition, transient hypocalcemia has been reported especially following the first infusion and it can cause symptoms in rare cases. To prevent the development of symptomatic hypocalcemia, the parent or guardian of each child will receive an information sheet and all patients will receive calcium supplementation at the doses recommended in Table 5-1 starting from the day of infusion and for a minimum of 5 days after each infusion (for sites where this calcium supplementation usually starts prior to the infusion, the total treatment period is approximately 10 days in total) (Hogler et al 2004).

5.2 Treatment arms

At Visit 1, all patients will be counselled regarding adequate dietary intake of calcium and vitamin D with or without supplementation. At Visit 2, each patient will be randomized in a

1:1 ratio within one of two treatment arms to receive either twice yearly 0.05 mg/ kg (max 5mg)i.v. infusion (at least 30 minutes) of zoledronic acid at randomization and Month 6 or twice yearly i.v. placebo at randomization and Month 6.

5.3 Treatment assignment and randomization

At Visit 2, all eligible patients will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the study drug.

The stratification of randomization will occur based on the baseline BMD value category: -2.0 or less vs. -2.0 to -1.0 vs. -1.0 to -0.5 at screening.

5.4 Treatment blinding

Patients, investigational staff, persons performing the assessments, Novartis clinical trial team and their agents, central laboratory, central imaging and data analysts will remain blinded to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study, (2) the identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration and appearance.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.9) and at the conclusion of the study.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.5.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 00001, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number

00002, the third patient is assigned patient number 00003). The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Only the assigned patient number should be entered in the field labeled "Patient ID" on the EDC data entry screen (e.g. enter '00001', '00002', etc.). Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomized for any reason, the IRT must be notified within 2 days that the patient was not randomized. The reason for not being randomized will be entered on the Screening Log, and the Demography CRF pages should also be completed. The patient numbers are already created into eCRF. This patient number should be used in all documents or request forms for vendors.

e.g.: site 0001 patient number 00002 will have the subject number 000100002.

Additional information to be collected on Screening Failures is described in Section 6.1. A patient who is rescreened should be assigned the next consecutive number.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

The study medication packaging has a 2-part label. A unique randomization number is printed on each part of this label which corresponds to one of the 2 treatment arms. Investigator staff will identify the study drug package to dispense to the patient by calling the IRT and obtaining the medication number. Immediately before dispensing the package to the patient, the investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the

completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

At physician's discretion, vitamin D and calcium supplementation may be managed by diet alone, and this should be recorded in the source records.

When dietary supplements are recommended, this non-study treatment has to be recorded in the Concomitant medications/Significant non-drug therapies eCRF, specifically:

- Calcium supplements at the time of infusion (all patients)
- Multivitamins that contain the RDA for calcium and vitamin D from Visit 1 to Visit 8 in line with Table 5-1
- Calcium or calcium plus vitamin D supplements from Visit 1 to Visit 8 in line with Table 5.1
- Vitamin D as a single supplement from Visit 1 to Visit 8 in line with Table 5.1

Details are described in the CRF completion guidelines.

5.5.4 Instructions for prescribing and taking study treatment

All kits of study treatment assigned by the IRT will be recorded/databased in the IRT.

Patients will receive a single dose of zoledronic acid or placebo of 0.05 mg/ kg, administered as a slow infusion of 100 mL over at least 30 minutes, at Visit 2 and Visit 5 as follows:

AGE	DOSE of ZOLEDRONIC ACID	TIME OF INFUSION
≥ 5 years to ≤ 17 years	0.05 mg/kg diluted in 100 mL of NS	30 minute infusion

The zoledronic acid or placebo dose is not to exceed 5.0 mg

A peripheral intravenous line must be used for the ZOL or placebo infusion. The i.v. infusion will be preceded by and followed by a 10 mL normal saline flush of the intravenous line.

As an example, the following table demonstrates how to prepare drug for a patient who weighs 46 kg.

Table 5-2 Preparation of iv zoledronic acid or placebo infusion

Patient Weight (kg)	Patient dose based on 0.05 mg/kg	Total number of 5.0 mg/100mL vials	Volume of ZOL or placebo to add to the normal saline	Volume of normal saline	Total volume of prepared infusion
46 kg	Y = 2.3 mg	1 vial	46 mL	100 mL	146 mL
X kg	X kg * 0.05 mg/kg = Y or Patient dose	1 vial	Y / 5mg/100mL= Patient dose	100 mL	100 mL + volume of reconstituted ZOL or placebo to add
Note: The maximum dose is 5 mg therefore the maximum volume from the 5mg/100mL ZOL/placebo vial to be used in this study is 100mL					

Preparing the patient for the infusion

In the event of a recent fracture, at least 1 month should elapse between the fracture and infusion of study drug. In the event of surgery to bone, at least 3 months should elapse between the procedure and infusion of study drug.

Before the first infusion of study treatment, both the local ionized calcium and serum creatinine should be within normal limits. Further details are provided in the Trial Master File.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Investigational or other treatment dose adjustments and/or interruptions are not permitted.

5.5.6 Rescue medication

Not applicable.

5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the concomitant medications / significant non-drug therapies eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

5.5.7.1 Treatment of study drug related adverse events:

As with other bisphosphonates, zoledronic acid has been associated with post-dose symptoms that may include fever, nausea, myalgia, arthralgia and bone pain, with onset occurring within the first 72 hours after the infusion. Typically these symptoms occur with the first infusion of bisphosphonate. The symptoms are usually mild to moderate and rarely severe. These symptoms may be adequately managed, at the discretion of the investigator, with non-steroidal anti-inflammatory agents (e.g. acetaminophen/paracetamol or ibuprofen) and/or anti-emetics by local treatment standards and according to approved local labeling. Based on data from controlled trials, treatment with non-steroidal anti-inflammatory agents will reduce the incidence of these symptoms by approximately 50%. In managing these symptoms it is important to encourage adequate hydration and food intake.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the concomitant medications/significant non-drug therapies CRF after start of study treatment.

5.5.8 Prohibited medication

Use of the following treatments is NOT allowed throughout the duration of the trial: bisphosphonates, denosumab, high dose sodium fluoride and nephrotoxic drugs e.g. methotrexate.

5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- patient number

In addition, oral and written information must be provided to the patient/parent/guardian on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

5.6 Study Completion and Discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed all the assessments in the last visit planned in the protocol (Visit 8, Month 12).

Continuing care should be provided by investigator and/or referring physician based on patient availability for follow-up. This care may include:

- Enrollment in the extension study: Patients who complete the 12 month study will be offered a 12 month extension study where all patients will receive zoledronic acid CZOL446H2337E1.
- Alternative therapy may be prescribed at the discretion of the treating physician at Month 12.

5.6.2 Discontinuation of Study Treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration i.e. before Visit 5, Month 6, and can be initiated by either the patient or the investigator.

The investigator must discontinue study treatment for a given patient if he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Patient's wish
- Pregnancy (see Section 6.5.5 and Section 7.4)
- Use of prohibited treatment as per recommendations in Section 5.5.8
- Any situation in which study participation might result in a safety risk to the patient
- Emergence of the following adverse events:
  - Osteonecrosis of the jaw
  - Renal failure
  - Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study

If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study. The patient should return to the clinic as soon as possible, after discontinuation of study drug, for a study treatment discontinuation visit. Treatment discontinuation visit assessments detailed in Visit 8, Month 12 in Table 6-1 should be completed and recorded in the CRF. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the Dosage administration record CRF.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should to be collected at clinic visits or via telephone visits:

- new / concomitant treatments
- adverse events/serious adverse events

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient, preferably according to the study visit schedule.

The investigator must contact the IRT to register the patient's discontinuation from study treatment.

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9

5.6.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information in the source document.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in Table 6-1.

5.6.4 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed.

Patients must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

Table 6-1 Assessment schedule

Period	**Screen**	**Treatment**						
Visit	**1[18]**	**2**	**3**	**4[T]**	**5**	**6**	**7[T]**	**8 and TD and/or PSW**
Day	**-28**	**1[1]**	**10**	**90**	**180**	**190**	**270**	**365**
Month				**3**	**6**		**9**	**12**
Obtain parental informed consent (D) and assent (S)	x							
Medical history (D)	x	x						
Inclusion/exclusion criteria (S)	x	x						
Prior/concomitant medication, including GC (D)	x	x	x	x	x	x	x	x
Physical Exam (S)[8]	x	x			x			x
[redacted]								
Vital signs (D)[16]	x	x			x			x
Weight (D)	x	x			x			x
Tanner Staging (D), if applicable		x			x			x
Blood and urine for central laboratory analysis[2]	x	(x)	x		x	x		x
Pregnancy test, if applicable[3]	x	x		x[12]	x			x
Serum 25 (OH) vitamin D	x							x
Ionized calcium (local lab) (D)[5]		x						
Serum creatinine (local lab) (D)[9]	x	x						
Biomarkers (serum P1NP, NTX, BSAP, TRAP-5b)		x			x			x
Urine collection for PK (D)[17]								x
Pain assessment (D)[10]		x		x	x		x	x
DXA measurements[4,6]	x				x			x
X-ray[4,7,11]	x							x
AE/SAE(D)[15]	x	x	x	x	x	x	x	x
[redacted]								
Dispense calcium and vitamin D, if required	x	x			x			x
Contact IRT	x	x			x			x

Period	**Screen**	**Treatment**						
Visit	**1[18]**	**2**	**3**	**4[T]**	**5**	**6**	**7[T]**	**8 and TD and/or PSW**
Day	**-28**	**1[1]**	**10**	**90**	**180**	**190**	**270**	**365**
i.v. drug administration (ZOL/placebo) (D)		x			x			
[redacted]								
Study Completion form (D)								x

1 V1 lab results, including GFR should be available prior to V2

2 All randomized patients will have limited blood chemistry assessments, GFR & urinalysis performed at Visit 3 (10 days after Visit 2) and Visit 6 (10 days after Visit 5). An optional repeat at V2 is included, if the time between screening and V2 is close to 4 weeks.

3 Test to be performed for females with childbearing potential only. Serum test for central laboratory at screening and final visits, local urine test prior to infusion at Visits 2 and 5 – if positive, infusion should not be started.

4 Screening DXA and X-rays should be performed at Visit 1 to ensure the central imaging laboratory can provide status on patient eligibility; these assessments should be performed early in the screening process.

5 Ionized Ca measured pre-dose (local lab) only before the first infusion, if below normal range, treat and repeat test before study drug infusion, if visit needs to be re-scheduled inform the monitor.

6 Lumbar spine, total body and [redacted]

7 Lateral thoracolumbar spine and posteroanterior (PA) left hand/wrist (for bone-age assessment and cortical bone thickness)

8 Including an oral examination for exposed bone**.** At screening visit the PI will perform an oral exam and , if needed, will refer the patient to a dentist

9 For exclusion purposes if increase between Visits 1 and 2 greater than 0.5 mg/dL (44.2 µmol/L).

10 Pain is assessed using Faces Pain Scale-Revised (FPS-R)

11 An AP (anteroposterior) spine X-ray will be employed at screening, in order to identify fractures that may not be readily visualized on the lateral spine because of rotation/scoliosis/other

[12 Only sites where additional safeguards required: Supervised urine pregnancy test]

[redacted]

15 SAEs only to be collected from signing informed consent

16 Pulse rate and blood pressure only

17 Urine collection for PK: either an overnight sample, or collected over at least 4-hours during the day, for details, see Lab Manual

18 Screening visit can be on different days to permit scheduling of all investigations during the 28-day screening period

T = Telephone visit, S = Source documentation, D = Database, GC = Glucocorticoid, TD = study treatment discontinuation, PSW = Premature patient withdrawal

6.1 Information to be collected on screening failures

All patients who have signed informed consent but are not randomized will have the study completion page for the screening visit, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

Should the reason for non-eligibility change at a later clinic appointment e.g. treatment of vitamin D deficiency, deterioration in LS-BMD Z-score or worsening of fracture & etc., the child may be considered for re-screening, subject to medical approval from Novartis – see IRT guide and CRF completion guidelines for further details.

6.2 Patient demographics/other baseline characteristics

At the Screening visit, information on age, sex, race, and source of the referral will be collected. Relevant Medical History/Current medical conditions will be recorded and updated at Screening (Visit 1) and at Baseline (Visit 2), prior to the first dose of study medication. The time between Visit 1 and Visit 2 should be as close to 28 days as possible and must not extend beyond 8 weeks. Background information collected at Screening and/or Baseline will include:

- Details of current or past glucocorticoid therapy in the preceding 12 months prior to screening, including dose with start and stop dates
- Current and past concomitant medication
- Disease (chronic rheumatologic conditions, IBD, DMD, and others) related background/ historical information
- Other medical history and current medical conditions
- Trauma history, including history of falls
- Previous fracture history
- Tanner Pubertal Staging (Appendix 2)
- Vital signs and physical exams, including oral exam
- Pain assessment
- [redacted]
- [redacted]

Assessments collected at Screening will include:

1. AP and Lateral Thoraco-Lumbar X-ray to show evidence of vertebral fracture
2. Radiological films and radiological reports for suspected clinical fractures (as previously described in the inclusion criteria).
3. Posteroanterior left hand/wrist X-ray for bone-age and cortical bone thickness evaluation
4. DXA measurements
5. Central laboratory tests
6. Local laboratory test (serum creatinine)

6.3 Treatment exposure and compliance

Concomitant medications/Significant non-drug therapy prior to the first dose of study treatment and after start of study treatment will be collected in the CRF, including medication name and reason. More details (including dose and dates of intake) will be provided for the following categories of treatments: osteoporosis- related medications**,** nutritional supplements (vitamin D/ calcium), and glucocorticoids. A Dosage administration record will be completed for each i.v. dose of ZOL/placebo. Information collected will include the date of dose, start and stop times of infusion and the reason for each dose.

Compliance with vitamin D/ calcium will be assessed by the investigator and/or study personnel at each visit using information on diet, and supplement use provided by the patient/caregiver. All study treatment and any additional treatment (i.e. vitamin D and/or calcium provided by Novartis or designee) dispensed and returned must be recorded in the Drug accountability log.

6.4 Efficacy

6.4.1 Vertebral compression fracture

At Screening, AP and lateral X-rays of the lumbar and thoracic spine will be taken to evaluate the presence of vertebral fractures of Genant grade 1 or higher or radiographic signs of vertebral compression fracture. AP spine X-ray will be employed at baseline, in order to identify fractures that may not be readily visualized on the lateral spine because of rotation/scoliosis/other.

Radiographic signs of fracture include loss of endplate parallelism, vertebral buckling and endplate interruption. Patient's eligibility must be confirmed by the central imaging laboratory before the patient can be randomized. AP and lateral thoracolumbar spine X-rays taken within 1 month of Visit 1 (screening) can be used. The film and report must be sent to central imaging for fracture confirmation.

Lateral thoracolumbar spine X-ray will also be performed at the final visit (Visit 8) to assess incident vertebral fractures. Vertebral fractures present at baseline or occurring during the study will be defined according to the Semi-Quantitative (SQ) method and confirmed with the Quantitative Morphometric (QM) method for vertebral fracture assessment:

1. Mild (Grade 1) vertebral fracture is defined as greater or equal to **(≥)** 20% and less or equal to (≤) 25% reduction in anterior, middle, and/or posterior vertebral height.
2. Moderate (Grade 2) vertebral fracture is defined as greater than **(>)** 25% and less or equal to (≤) 40% reduction in any vertebral height.
3. Severe (Grade 3) vertebral fracture is defined as greater than **(>)** 40% reduction in any vertebral height.

or based on radiographic signs of vertebral compression fracture including loss of endplate parallelism, vertebral buckling and endplate disruption.

Specific instructions for sending radiographic images will be distributed to investigators prior to the start of study.

Vertebral morphometry (or concave index) will be calculated using the average ratio between mid-height and posterior height from L1 to L4 (Land et al 2006b)

6.4.3 DXA measurements

DXA measurements of the lumbar spine (LS), total body and [redacted] will be performed in all patients. LS-BMD Z-score, LS bone mineral content (BMC), Total Body BMC [redacted] will be assessed at Screening, Month 6 and Month 12. DXA will be acquired locally and the results will be sent to a central reader for evaluation. Detailed instructions will be provided in the DXA imaging manual.

6.4.4 Bone Marker Analysis

Specialized serum tests for BSAP, P1NP, TRAP-5b and NTX will be performed. Blood will be drawn from patients prior to receiving their first dose of study drug, at Month 6 and Month 12. Detailed shipping instructions will be provided in the Investigator Laboratory Manual.

6.4.6 Bone age assessment

Left posteroanterior (PA) hand/wrist X-ray will be taken at Visit 1 and at the Month 12 visit to assess bone age and the between-treatment differences for change in 2nd metacarpal cortical width at Month 12 relative to baseline.

If a fracture of the left upper extremity precludes radiographic imaging, then the right hand will be evaluated for this purpose. In this case, the right hand should be imaged at both Visit 1 and at Month 12. The information will be used in the assessment of bone density.

6.4.7 Pain assessment

Pain will be evaluated at each visit (in office and telephone visit) at randomization, Months 3, 6, 9 and 12. A FPS-R will be used for this purpose (Appendix 4).

6.4.8 Appropriateness of efficacy assessments

Fracture determination by X-ray is the standard endpoint for long-term studies in osteoporosis. However, in studies of 12 months duration, change in BMD has become an acceptable surrogate and has been shown to be a strong indicator of the efficacy of anti-resorptive therapies, including bisphosphonates such as ZOL. Bone marker assessments of change in BSAP, P1NP, TRAP-5b and NTX often parallel the change in BMD over the same time course. NTX and TRAP-5b measure bone resorption while BSAP and P1NP measure bone formation. In the growing child, [redacted] bone age also indicate the overall effectiveness of an intervention, but in this study, only trends may be observed over the 12 month period. Bisphosphonates are considered effective in managing bone pain, including fracture pain, and the FPS-R is a scale used to measure pain in children (Bieri et al 1990, Hicks et al 2001).

The efficacy measurements listed above are therefore expected to be appropriate for this study.

6.5 Safety

6.5.1 Physical examination

Physical examination, including an oral examination of the gums and roof of the mouth, will be performed at Screening, Baseline (pre-dose, Visit 2), Month 6 and Month 12. If the investigator is concerned about the patient's oral health then the patient may be referred to a dentist.

Significant findings that are present prior to the first infusion of study drug must be included in the Relevant Medical History CRF or current medical conditions CRF. Significant findings made after the start of study drug which meet the definition of an AE must be recorded in the AE CRF.

Tanner staging will be performed at Visit 2 (baseline), Month 6 (second dose) and the end of study (EOS)/Month 12 visit.

6.5.2 Vital signs

Measurements will be made of sitting blood pressure and pulse rate at Visits 1, 2 (pre-dose), Month 6 (pre-dose) and Month 12.

Clinically notable vital signs are defined in Appendix 1.

6.5.3 [redacted] weight

Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be performed at Visits 1, 2, Month 6 and Month 12 and recorded on the Vital sign CRF.

[redacted]

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected except for ionized calcium and serum creatinine (for exclusion purposes). Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1.

EMLA cream may be used at all blood draws. EMLA Cream is a topical anesthetic which numbs the skin and decreases the sensation of pain. There should be up to three attempts to obtain a serum sample from the patient at any blood draw.

A central laboratory will collect and evaluate blood and urine samples for hematology, biochemistry and urinalysis at screening (Visit 1), Month 6 (Visit 5) and Month 12 (Visit 8).

A repeat at Visit 2 may be needed if the time between screening and Visit 2 is close to or more than 4 weeks and/or the Visit 1 result was close to the limits of the normal range.

Patients with laboratory tests containing clinically significant abnormal values will be followed regularly until the values return to normal ranges or until a valid reason for the abnormality, other than study drug related adverse event, is identified.

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential counts, and platelet count will be measured.

6.5.4.2 Clinical chemistry

Non-fasting specimens will be obtained for glucose, creatinine, serum urea, uric acid, total protein, SGOT (AST), SGPT (ALT), alkaline phosphatase, sodium, potassium, chloride, phosphorus, magnesium, albumin, and calcium.

Specialized (non-fasting) testing for serum 25-hydroxy vitamin D will be performed at screening (Visit 1) and Month 12 (Visit 8).

Glomerular Filtration Rate (GFR) will be calculated using the Schwartz formula at all visits where serum creatinine will be measured (Visits 1, 3, 5, 6 and 8) by the central laboratory.

Schwartz Formula to calculate Glomerular Filtration

GFR (mL/min/1.73 m^2) = k [Height (m)] / Serum Creatinine (mg/dL)

k = Constant

k=0.41

Additional renal and calcium monitoring will be performed 10 days after each study drug infusion (Visit 3 and Visit 6).

Local laboratory evaluation of serum creatinine will be performed at Visits 1 and 2, if there is an increase greater than 0.5 mg/dL (44.2 µmol/L), the patient should be excluded.

Serum ionized calcium will be evaluated in the local laboratory at pre-dose (first infusion). If the result is close to or below the lower limit of the normal range, the infusion must be delayed until the value has returned to normal.

6.5.4.3 Urinalysis

A urine specimen will be obtained at Visits 1, 3, 5, 6 and 8 for routine urinalysis, including microscopic examination.

6.5.5 Pregnancy and assessments of fertility

Serum pregnancy tests (β-hCG) will be performed at screening (Visit 1) and at the final visit (Visit 8). Urine pregnancy tests will be performed at Visit 2 and Visit 5, prior to the study drug infusion. The test will be conducted for all female patients of childbearing potential. If menarche occurs during the study, a pregnancy test should be performed at the first visit following the first period.

[For sites where additional safeguards are required only due to local regulations e.g. UK, Italy, Germany, Sweden & etc., an additional supervised urine pregnancy test is required at Visit 4, 90 days after first study drug administration). In case of a positive test, the patient must contact the investigator immediately.]

6.5.6 Bone Safety Monitoring

Measurement of LS-BMD Z-score at Visits 5 and 8 (months 6 and 12) will be subject to monitoring from the central imaging lab for the detection of excessive changes in BMD. Repeat scans may be requested if technical factors are suspected to be involved. The investigator will be notified in the case of an absolute change in LS-BMD greater than -0.5 compared with screening at the Month 6 or 12 visits or an absolute increase of LS-BMD of greater than +2.0. In either event, the investigator should further assess the patient for secondary causes (e.g. underlying disease). If it is in the best interests of the patient to discontinue the study, discontinuation procedures should be followed as described in Section 5.6.2

6.5.7 Appropriateness of safety measurements

Safety assessments consist of monitoring and recording of all adverse events and serious adverse events, including those known to be associated with bisphosphonate use; renal function (serum creatinine and GFR), regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations including oral examinations for exposed bone. An oral examination of the gums and roof of the mouth, will be performed as part of the physical examination at screening, randomization, Month 6 and Month 12 visits to assess for signs of ONJ. ONJ is characterized by exposed bone in the maxillofacial area that occurs in association with dental surgery, or occurs spontaneously, with no evidence of healing. See Section 3.6.

Tanner staging assesses the sexual maturity of the patient and is important to indicate child-bearing potential in girls as these girls will require pregnancy tests before each infusion.

Vitamin D (25-hydroxy-D) and calcium will be measured at Visit 1 to ensure that all patients have adequate vitamin D and calcium levels at study entry, as a precaution to minimize the risk of developing hypocalcemia with the first zoledronic acid administration. In addition, ionized calcium will be monitored locally, before the first infusion to ensure that the patients have normal serum calcium level. Families will be counselled on the importance of a diet rich in calcium and vitamin D, and supplements recommended based at the investigators discretion.

Bone safety is monitored by the central imaging laboratory via DXA at Month 6 and 12. In case of excessive change in BMD Z-scores compared with screening, the investigator will be alerted.

The safety assessments selected are standard for this indication/patient population.

6.6 Other assessments

6.6.3 Pharmacokinetics

Further details on sample collection, numbering, processing and shipment can be found in the Laboratory Manual

Urine will be collected into a polypropylene container during at least a 4-hour sampling period at Visit 8 (Month 12). The first morning sample may be used if the time of the previous night's bladder voiding is recorded, otherwise it should be discarded (see Laboratory Manual for further details).

All samples will be given a unique sample number. The actual sample collection date and time will be entered on the PK urine collection page of the eCRF.

Pharmacokinetic analytical method

Zoledronic acid will be determined in urine by a validated radio-immunoassay method. The Lower Limit of Quantification (LLOQ) is 10 ng/mL. Concentrations below the LLOQ will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report.

Pharmacokinetics parameters

Aet1-t2 will be calculated as Aet1-t2 = urine volume (t1-t2) × urine concentration.

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

In this protocol, due to the long screening period (at least 4 weeks), although SAEs are collected from signing the informed consent, the AE page of the eCRF is only completed from the first day of study drug. In the case of randomized patients only, any events that occur prior to receiving study treatment, should be recorded in the eCRF as Medical History.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity grade
    - mild: usually transient in nature and generally not interfering with normal activities
    - moderate: sufficiently discomforting to interfere with normal activities
    - severe: prevents normal activities

There may be cases where a severe AE that is life-threatening may not necessarily be an SAE (e.g. certain laboratory abnormalities in the absence of meeting other seriousness criteria).

- its relationship to the
    - study treatment (no/yes), or
    - other treatment (no/yes). or
    - both or indistinguishable
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE)
- action taken regarding investigational treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- investigational treatment dosage adjusted/temporarily interrupted

- investigational treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

All diagnosed cases of ONJ should be considered as "medically significant" irrespective of whether the event meets the definition of "Serious Adverse Event" under current health authority guidelines. These cases are therefore reported to Novartis Drug Safety and Epidemiology as well as local health authorities under the guideline of SAE reporting.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse event.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs *(either initial or follow up information)* is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to *each specific component of study treatment (if study treatment consists of several components)* complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the

fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE

Follow-up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes,	Yes, even if not associated with a SAE

7.4 Pregnancy reporting

There are no adequate data on the use of zoledronic acid in pregnant women. Studies in animals with zoledronic acid have shown reproductive toxicological effects including

malformations. Teratology studies were performed in two species, both via subcutaneous administration. Teratogenicity was observed in rats at doses greater than or equal to 0.2 mg/kg and was manifested by external, visceral and skeletal malformations. Dystocia was observed at the lowest dose (0.01 mg/kg body weight) tested in rats. No teratological or embryo/fetal effects were observed in rabbits, although maternal toxicity was marked at 0.1 mg/kg due to decreased calcium levels. No risks in males were identified. The potential risk for humans is unknown. Despite this theoretical risk, there have been no human reports to date of an adverse effect of bisphosphonates when administered either pre-conception or during pregnancy. This appears to stem from the fact that the amount of bisphosphonate that is mobilized from the skeleton is clinically insignificant is supported by numerous human reports of bisphosphonate administration pre-conception/during pregnancy and newborn outcomes (Levy 2009 and Djokanovic 2008).

[For sites where additional safeguards are required only e.g. UK, Italy, Germany, Sweden & etc.: If the patient is a female of child bearing potential, the investigator must ensure that patient and parent(s)/guardian(s):

- understands the theoretical teratogenic risk
- understands the need for follow-up (e.g. pregnancy testing) on a regular basis
- has used at least one and preferably two methods of effective contraception including a barrier method for at least 2 months prior to screening and is continuing to use effective contraception throughout the duration of the trial and for at least 1 year after the end of the trial
- understands and accepts the need for effective contraception
- follows the advice on effective contraception, even if patient has amenorrhea
- is capable of complying with effective contraceptive measures
- is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
- has acknowledged the precautions associated with the use of zoledronic acid.]

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

8 Data review and database management

8.1 Site monitoring

Before study initiation, either at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs. The investigator must also keep the original informed consent form signed by the patient or parent(s)/guardian(s) [a signed copy is given to the patient or parent(s)/guardian(s)].

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Oracle Clinical/Remote Data Capture (OC/RDC) system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff (or CRO working on behalf of Novartis) review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

DXA and X-ray data will be processed centrally through a central imaging vendor and the results will be sent electronically to Novartis.

Bone-marker analysis will be processed centrally through a central laboratory vendor and the results will be sent electronically to Novartis.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be implemented to safeguard patient safety. All members will be independent from the sponsor and study investigators. The DMC will conduct regularly scheduled meetings to review study progress and any potential emerging safety signals in the study population.

9 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

9.1 Analysis sets

9.1.1 Intention-to-treat (ITT) population

The ITT population will consist of all patients randomized. Following the ITT principle, patients will be analyzed according to the treatment they were assigned to at randomization.

9.1.2 Modified Intention-to-treat (MITT) population

The MITT population will consist of all patients in the ITT population who have an evaluable baseline assessment for the endpoint of interest.

Patients will be included in the MITT population for the analysis of the primary efficacy endpoint (change in lumbar spine Z-score at Month 12 relative to baseline) if their DXA assessments includes baseline and at least one post-baseline LS-BMD score.

According to the ITT principle, patients will be analyzed with respect to the treatment to which they were randomized.

9.1.3 Per-protocol (PP) population

The PP will include all patients in the ITT population who do not have any major protocol deviations. Prior to unblinding, the Clinical Trial Team and Trial Statistician will identify the major protocol deviations that will exclude patients from the PP population.

9.1.4 Safety population

The Safety Population will consist of all patients that have been exposed to at least one infusion of study drug. Patients will be analyzed according to treatment received.

9.2 Patient demographics and other baseline characteristics

Appropriate summary statistics for the demographic and other baseline characteristics variables will be provided for the ITT and MITT populations. In addition, the baseline comparability between treatment groups will be evaluated for demographic and other baseline characteristics variables. Categorical variables will be evaluated using Fisher's exact test, and the continuous variables will be evaluated using a Wilcoxon rank-sum test.

Note that these tests of comparability are performed for descriptive purpose only, and will not be considered to define any formal basis for determining factors which should be included in statistical analysis models. However, when these tests yield significant results they can be used as extra information in interpreting any treatment-by-factor interactions that are observed in the sensitivity analyses performed on the primary and secondary efficacy variables.

9.3 Treatments

9.3.1 Study drug and compliance

Descriptive statistics will be provided by treatment group for duration of infusion and volume of infusion.

Summary statistics will be provided for the percentage of calcium taken post-infusion and the duration of exposure by treatment group.

9.3.2 Concomitant therapy

Concomitant medications will be coded using the WHO Drug Reference List that employs the Anatomical Therapeutic Chemical classification system. Summary tables will be provided that present the number and percent of patients receiving those medications by preferred term and treatment after start of study drug administration. The medications will be sorted in decreasing order of frequency with respect to usage in the zoledronic acid group.

Descriptive summary statistics (mean, median, standard deviation, minimum, maximum) will be provided for the dose and duration of use of glucocorticoids by treatment group at baseline and during the 12-month double-blind period. Descriptive summary statistics (mean, median, standard deviation, minimum, maximum) will also be provided for the duration of exposure to glucocorticoid treatment between randomization and the end of double-blind treatment. The number and percentage of patients receiving different types of glucocorticoid therapy will be presented by preferred term and treatment group.

Usage of calcium and vitamin D will be summarized by treatment group with respect to the forms of calcium and vitamin D taken.

9.4 Analysis of the primary variable

9.4.1 Variable

The primary efficacy variable will be the change in LS-BMD Z-score at Month 12 relative to baseline, in patients treated with twice yearly i.v. ZOL compared to patients treated with placebo. It is derived as (LS-BMD Z-score at Month 12 – LS-BMD Z-score at baseline).

9.4.2 Statistical model, hypothesis, and method of analysis

The primary efficacy objective is to demonstrate superiority with respect to the change in LS-BMD Z-score at Month 12 relative to baseline in patients treated with zoledronic acid compared to patients receiving placebo.

Let μ_Z and μ_P be the population mean of the change in LS-BMD Z-score at Month 12 relative to baseline for patients treated with ZOL and patients receiving placebo, respectively. The null hypothesis of no difference between treatment groups ($H_0 : \mu_Z = \mu_P$) will be tested against the alternative hypothesis that there is difference between treatment groups ($H_A : \mu_Z \neq \mu_P$). The tests will be done at a nominal significance level of $\alpha = 0.05$.

The primary efficacy objective will be demonstrated by showing that the t test statistic, $\frac{|d|}{SE}$, is greater than $t_{df,0.975}$ in the modified intent-to-treat population, where d and SE are the estimated treatment difference and the estimated standard error of d from an analysis of covariance (ANCOVA) model with treatment, pooled centers, underlying condition treated with glucocorticoids and baseline LS-BMD Z-score as explanatory variables, df is the associated degrees of freedom computed from the error term in the model, and $t_{df,0.975}$ is the

97.5% quantile of the t distribution with *df* degree of freedom. The test and confidence intervals based on this test statistic are robust to the assumptions of normality and of equal variances when within-center treatment group sample size are equal, which is generally the case that treatment allocation is nearly equal within each center because of the manner in which the randomization is carried out. Nevertheless, the underlying assumption of normality and variance homogeneity for the primary analyses will be reviewed and tested by Shapiro's test and Levene's test, respectively, prior to unblinding the data. If the underlying assumption is violated, a transformation or non-parametric approach, such as van Elteren or Cochran-Mantel-Haenszel test (CMH2 from SAS procedure PROC FREQ) adjusted for center, will be applied to the data as appropriate for the hypothesis evaluated.

9.4.3 Handling of missing values/censoring/discontinuations

In the modified intent-to-treat population, last observation carried forward (LOCF) will be used to impute a value for LS-BMD Z-score at Month 12 for any patient who does not have a Month 12 assessment; however, if a patient prematurely discontinues from the study during the double-blind phase without providing any LS-BMD measurements at Month 6 or Month 12, then a zero percent change in LS-BMD will be assumed at Month 12.

Given that a pediatric population is being studied and patients are expected to experience bone growth during the study, an assumption of zero change over 12 months and LOCF from Month 6 measurements would be considered conservative.

9.4.4 Sensitivity analyses

Confirmation of the result for the primary efficacy variable will be performed using the per-protocol population without imputation for missing data using the ANCOVA model applied for the primary efficacy analysis.

As another supportive analysis to the primary analysis, the change in LS-BMD Z-score at Month 12 relative to baseline will be compared using the analysis of covariance model with treatment, pooled centers, underlying condition treated with glucocorticoids, baseline LS-BMD Z-score and treatment-by-center interaction as explanatory variables to explore treatment-by-center interactions using the MITT population. If $p < 0.1000$ for the treatment-by-center interaction test, then, in addition, further work will be done (tabular and/or graphical presentations) as necessary to look for a possible explanation to the differences observed across centers. Tabular and graphical presentations will also be presented as necessary to explain interactions if they exist for underlying condition and baseline pubertal status. Additional prognostic factors will be evaluated as necessary descriptively and in model fitting.

In addition, a responder analysis will be done by comparing the proportion of patients who increase their lumbar spine z-score at Month 12 in the ZOL group relative to the placebo group using the MITT population. Between-treatment differences will be evaluated using a logistic regression model with treatment, pooled centers, underlying condition treated with glucocorticoids and baseline LS-BMD Z-score as explanatory variable.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The analyses of secondary [redacted] efficacy variables will be performed on the MITT population without imputation for missing values unless specified otherwise. Descriptive statistics (mean, median, standard deviation, minimum and maximum) will be presented by treatment group for each continuous variable and the number and percentage of patients will be presented by treatment group for each categorical variable, unless otherwise specified. All hypothesis tests will be evaluated at a 0.05 level of significance, and the p-values will be rounded to the 4th decimal place. Adjustment for multiple comparisons will not be made for any of the secondary efficacy variables since none of these variables is intended to be used for any promotional claims. If changes are made to this plan, appropriate adjustments for multiplicity will be included as part of the report analysis plan (RAP) prior to clinical database lock.

The secondary efficacy variables and their analysis methods are described below.

9.5.1.1 Change in lumbar spine BMD Z-score at Month 6 relative to baseline

The change in LS-BMD Z-score at Month 6 relative to baseline between zoledronic acid and placebo will be evaluated using an ANCOVA model with treatment, pooled centers, underlying condition treated with glucocorticoids and baseline LS-BMD Z-score as explanatory variables.

9.5.1.2 Change in lumbar spine and total body BMC at Months 6 and 12 relative to baseline

The change in BMC at the lumbar spine and total body at Month 6 and Month 12 relative to baseline between zoledronic acid and placebo will be evaluated using an ANCOVA model with treatment, pooled centers, underlying condition treated with glucocorticoids and baseline BMC as explanatory variables.

9.5.1.3 Relative change in biochemical markers of bone turnover (Serum NTX, TRAP-5b, BSAP and P1NP)

A transformation of the log ratio of treatment value vs. baseline value (calculated by dividing the post-baseline value by the baseline value and then applying the $\log_e$ transformation) at each visit will be used to normalize the distribution of the biochemical marker parameters. An ANCOVA model with treatment group, pooled centers, underlying condition treated with glucocorticoids, and $\log_e$ (baseline value), as explanatory variables will be performed on the transformed data at each post-baseline time point.

The 2-sided 95% confidence intervals in difference of transformed data between zoledronic acid and placebo will be constructed using the same method as described for the primary analysis based on the described ANCOVA model. In addition, the 2-sided 95% confidence intervals obtained from the model will be back transformed to the original scale.

9.5.1.4 Incidence of new vertebral fractures at Month 12

The number and percentage of patients with new vertebral fractures at Month 12 will be presented by treatment group. Between-treatment differences will be evaluated using Fisher's exact test.

9.5.1.5 Change in vertebral morphometry at Month 12 relative to baseline

The change in vertebral morphometry at Month 12 relative to baseline will be evaluated using an ANCOVA model with treatment, pooled centers, underlying condition treated with glucocorticoids and baseline value as explanatory variables

9.5.1.6 Change in metacarpal cortical width at Month 12 relative to baseline

The change in metacarpal cortical width at Month 12 relative to baseline will be evaluated using an ANCOVA model with treatment, pooled centers, underlying condition treated with glucocorticoids and baseline value as explanatory variables

9.5.1.7 Reduction in pain from baseline

The reduction in pain from baseline by visit will be evaluated based on whether or not patients have a decrease in their Faces Pain Scale-Revised from baseline. If pain remains the same or worsens from baseline a patient will be classified as '0' and if the pain scale decreased then the patient will be classified as '1'. Whether or not a patent experiences a decrease in pain will be evaluated using a logistic regression model with treatment, pooled centers, underlying condition treated with glucocorticoids and baseline pain score as explanatory variables.

9.5.2 Safety variables

9.5.2.1 Adverse event

The number and percentage of patients who report adverse events will be summarized within each sub-population by treatment group according to primary system organ class (PSOC), preferred term, and severity. If a patient reports more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a patient reports more than one adverse event within the same PSOC, the patient will be counted only once with the adverse event of greatest severity.

Death, serious adverse events, adverse events causing permanently discontinuation of study drug, and adverse events cause action taken will be presented by treatment group. Listings of these events will be provided.

9.5.2.2 Laboratory evaluations

The summary of laboratory evaluations will be presented with respect to three groups of laboratory tests (hematology, serum chemistry, and urinalysis).

Descriptive summary statistics (mean, median, standard deviation, minimum and maximum) for the baseline, each study visit, and change from baseline to each study visit will be presented. These descriptive summaries will be presented by laboratory test group and treatment group within each sub-population.

In addition, shift tables will be provided in order to compare a patient's baseline laboratory evaluation relative to each study visit. For the shift tables, the normal laboratory values will be used to evaluate whether a particular laboratory test value is normal, low, or high for each visit value relative to whether or not the baseline value is normal, low, or high. These summaries will be presented by laboratory test group and treatment group within each sub-population.

9.5.2.3 Vital signs

The number and percentage of patients who have vital sign values that meet the criteria for being clinically notable after the first dose of study medication, will be presented by treatment group, within each subpopulation. Patient listings will be also provided that presents each patient's vital sign profile for those tests that are outside of the clinically notable ranges.

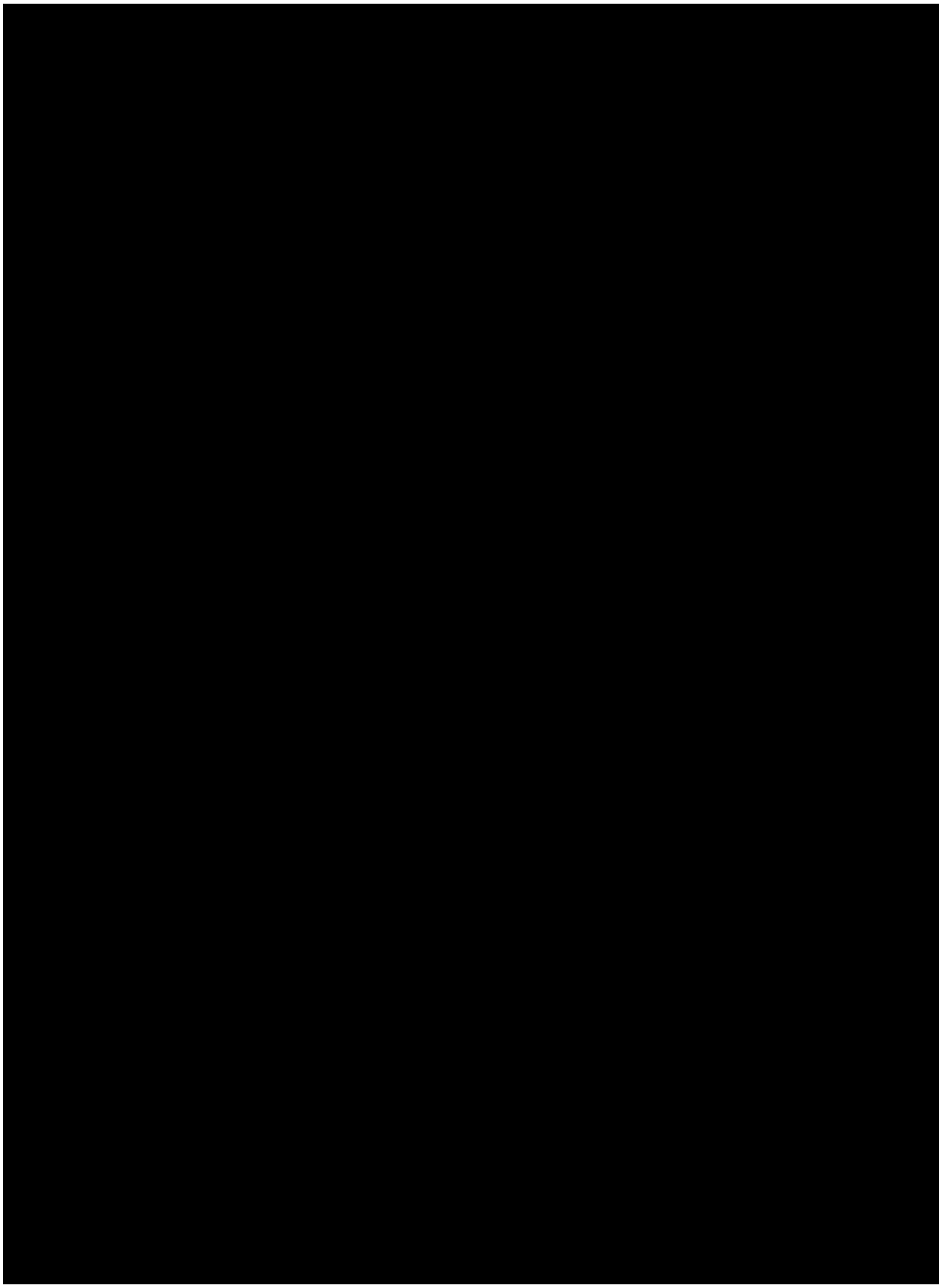
9.5.3 Pharmacokinetics

ZOL446 urine concentration data will be listed by treatment, subject, and visit/sampling time point.

Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics. A geometric mean will not be reported if the dataset includes zero values.

Pharmacokinetic parameters will be calculated as described in Section 6.6.3 and will be listed by treatment and subject. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum.



9.7 Interim analyses

It is not intended that an interim analysis will be conducted for this study.

9.8 Sample size calculation

The sample size is calculated to show superiority of zoledronic acid relative to placebo at Month 12.

The null hypothesis of no difference between treatment groups in the mean change in LS-BMD Z-score at Month 12 relative to baseline. In testing this hypothesis, it is assumed that the standard deviations for the two treatment groups is 0.93 under H_0 and H_A. Based on a primary endpoint of the change in LS-BMD Z-score at 12 months relative to baseline assuming a 0.63 increase in LS-BMD Z-score over 12 months with zoledronic acid and no change in the LS-BMD Z-score in the placebo group and a common standard deviation of 0.93, 82 patients are required to show a significant increase in LS-BMD Z-score at the 0.05 level with 85% power. Adjusting for a dropout rate of 10%, approximately 46 patients per treatment group are required.

The amount of information from controlled trials in a pediatric GIO population is limited. The 0.63 increase in LS-BMD Z-score is based on the increase observed with pamidronate-treated children on chronic glucocorticoid therapy presented in (Acott et al 2005). The common standard deviation of 0.93 was estimated from the pamidronate-treated children and untreated control evaluated in (Acott et al 2005). This standard deviation is consistent with the estimate of the standard deviation obtained from the zoledronic acid group of pediatric osteogenesis imperfecta patients in Study CZOL446H2202. Therefore, it is inferred that the assumption of a 0.63 increase in LS-BMD Z-score over 12 months with ZOL is acceptable.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so or a child who is not legally allowed to do so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Investigators will be provided by Novartis, a proposed model informed consent form that complies with the ICH GCP guideline and regulatory requirements which is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC and a copy of the approved version must be provided to the Novartis monitor or designee after IRB/IEC approval.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

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13 Appendix 1: Clinically notable laboratory values and vital signs

The laboratory results are accessible by Novartis when the results have been sent to the investigators. Clinically significant changes should be recorded in the CRF as either Medical History, AE or SAE.

Laboratory parameter	Units	Age/gender range	Normal range	Criteria for clinically significant change
Systolic Blood Pressure	mmHg	< 12 yrs	(70.0, 125.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		12 yrs/male	(90.0, 127.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		13 yrs/male	(90.0, 130.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		14 yrs/male	(90.0, 132.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		15 yrs/male	(90.0, 135.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		16 yrs/male	(90.0, 138.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		17 yrs/male	(90.0, 140.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		12 yrs/female	(90.0, 126.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		13 yrs/female	(90.0, 128.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		14 yrs/female	(90.0, 130.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change

Laboratory parameter	Units	Age/gender range	Normal range	Criteria for clinically significant change
		15 yrs/female	(90.0, 131.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		16 yrs/female	(90.0, 132.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
		17 yrs/female	(90.0, 132.0)	If within the normal range at baseline, a value outside of normal range along with at least a 20 unit change
Diastolic Blood Pressure	mmHg	< 12 yrs	(40.0, 85.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		12 yrs/male	(50.0, 83.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		13 yrs/male	(50.0, 84.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		14 yrs/male	(50.0, 85.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		15 yrs/male	(50.0, 86.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		16 yrs/male	(50.0, 87.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		17 yrs/male	(50.0, 89.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		12 yrs/female	(50.0, 82.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		13 yrs/female	(50.0, 84.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change

Laboratory parameter	Units	Age/gender range	Normal range	Criteria for clinically significant change
		14 yrs/female	(50.0, 85.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		15 yrs/female	(50.0, 86.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		16 yrs/female	(50.0, 86.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		17 yrs/female	(50.0, 86.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
Heart Rate	bpm	< 12 yrs	(70.0, 130.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
		≥ 12 yrs	(50.0, 120.0)	If within the normal range at baseline, a value outside of normal range along with at least a 15 unit change
Blood Urea Nitrogen	mg/dL	≤ 17 yrs	(4.0, 24.0)	Outside the normal range
Calcium	mg/dl	> 2 - 17 yrs	(8.4, 10.3)	Outside the normal range
Chloride	mEq/L	≤ 17 yrs	(94.0, 112.0)	Outside the normal range
Creatinine	mg/dl	5 - 7 yrs/ Female	(0.2, 0.5)	Outside the normal range
		> 7- 10 yrs/ Female	(0.2, 0.6)	Outside the normal range
		> 10 - 13 yrs/ Female	(0.3, 0.7)	Outside the normal range
		> 13 - 16 yrs/ Female	(0.4, 0.8)	Outside the normal range
		> 16 - 17 yrs/ Female	(0.5, 0.9)	Outside the normal range
		5 - 7 yrs/ Male	(0.2, 0.5)	Outside the normal range
		> 7- 10 yrs/ Male	(0.3, 0.6)	Outside the normal range
		> 10 - 13 yrs/ Male	(0.3, 0.7)	Outside the normal range
		> 13 - 16 yrs/ Male	(0.4, 0.8)	Outside the normal range
		> 16 - 17 yrs/ Male	(0.5, 0.9)	Outside the normal range

Laboratory parameter	Units	Age/gender range	Normal range	Criteria for clinically significant change
Magnesium	mg/dl	5 - 7 yrs/ Female	(1.7, 2.2)	Clinically significantly low, if < 1.0 mg/dL
		> 7- 10 yrs/ Female	(1.6, 2.2)	Clinically significantly low, if < 1.0 mg/dL
		> 10 - 13 yrs/ Female	(1.6, 2.2)	Clinically significantly low, if < 1.0 mg/dL
		> 13 - 16 yrs/ Female	(1.6, 2.3)	Clinically significantly low, if < 1.0 mg/dL
		> 16 - 17 yrs/ Female	(1.5, 2.2)	Clinically significantly low, if < 1.0 mg/dL
		5 - 7 yrs/ Male	(1.7, 2.4)	Clinically significantly low, if < 1.0 mg/dL
		> 7- 10 yrs/ Male	(1.6, 2.2)	Clinically significantly low, if < 1.0 mg/dL
		> 10 - 13 yrs/ Male	(1.6, 2.2)	Clinically significantly low, if < 1.0 mg/dL
		> 13 - 16 yrs/ Male	(1.6, 2.3)	Clinically significantly low, if < 1.0 mg/dL
		> 16 - 17 yrs/ Male	(1.5, 2.2)	Clinically significantly low, if < 1.0 mg/dL
Potassium	mEq/L	> 1 - 17 yrs	(3.4, 5.4)	Outside the normal range
Phosphorus	mg/dl	5 - 10 yrs	(3.2, 6.1)	Outside the normal range
		> 10 - 15 yrs	(3.1, 6.0)	Outside the normal range
		> 15 - 17 yrs	(2.2, 5.1)	Outside the normal range
Sodium	mEq/L	$\leq$ 17 yrs	(132.0, 147.0)	Outside the normal range
Hemoglobin	g/dl	5 - 12 yrs/ Female	(11.2, 15.5)	Outside the normal range
		> 12 - 17 yrs/ Female	(11.6, 16.4)	Outside the normal range
		5 - 12 yrs/ Male	(11.2, 15.5)	Outside the normal range
		> 12 - 17 yrs/ Male	(12.7, 18.1)	Outside the normal range
ALT	u/L	5- 17 yrs	(6 , 200)	Outside the normal range
AST	u/L	5- 17 yrs	(10 , 200)	Outside the normal range
Alkaline Phosphatase	u/L	5- 17 yrs	(51 , 315)	Outside the normal range
Albumin	g/dL	5- 17 yrs	(2.9 – 4.7)	Outside the normal range
Hematocrit	%	5- 6 yrs/ Female	(35.0, 44.0)	Outside the normal range
		> 6 - 12 yrs/ Female	(34.0, 44.0)	Outside the normal range
		> 12 - 17 yrs/ Female	(34.0, 48.0)	Outside the normal range
		5 - 6 yrs/ Male	(33.0, 43.0)	Outside the normal range

Laboratory parameter	Units	Age/gender range	Normal range	Criteria for clinically significant change
		> 6 - 12 yrs/ Male	(34.0, 44.0)	Outside the normal range
		> 12 - 17 yrs/ Male	(39.0, 54.0)	Outside the normal range
RBC	10^6/uL	> 3 - 6 yrs/ Female	(4.1, 5.2)	Outside the normal range
		> 6 - 12 yrs/ Female	(3.7, 6.0)	Outside the normal range
		> 12 - 17 yrs/ Female	(4.1, 5.6)	Outside the normal range
		5- 6 yrs/ Male	(4.1, 5.3)	Outside the normal range
		> 6 - 12 yrs/ Male	(3.7, 6.0)	Outside the normal range
		> 12 - 17 yrs/ Male	(4.5, 6.4)	Outside the normal range
WBC	10^3/uL	5- 6 yrs	(4.00, 12.00)	Outside the normal range
		> 6 - 12 yrs	(4.35, 13.65)	Outside the normal range
		> 12 - 17 yrs	(4.35, 13.15)	Outside the normal range
Lymphocytes	10^3/uL	5- 6 yrs/ Female	(1.50, 8.00)	Outside the normal range
		> 6 - 12 yrs/ Female	(1.15, 6.65)	Outside the normal range
		> 12 - 17 yrs/ Female	(0.95, 5.25)	Outside the normal range
		5- 6 yrs/ Male	(1.50, 8.00)	Outside the normal range
		> 6 - 12 yrs/ Male	(1.15, 6.65)	Outside the normal range
		> 12 - 17 yrs/ Male	(0.95, 5.25)	Outside the normal range
Neutrophils	10^3/uL	5- 6 yrs/ Female	(1.00, 9.00)	Outside the normal range
		> 6 - 12 yrs/ Female	(1.35, 8.15)	Outside the normal range
		> 12 - 17 yrs/ Female	(1.65, 8.15)	Outside the normal range
		5- 6 yrs/ Male	(1.35, 8.65)	Outside the normal range
		> 6 - 12 yrs/ Male	(1.35, 8.65)	Outside the normal range
		> 12 - 17 yrs/ Male	(1.65, 8.15)	Outside the normal range
Eosinophils	10^3/uL	$\leq$ 17 yrs	(0.00, 0.57)	Outside the normal range

Lab normal ranges provided by Covance Labs

14 Appendix 2: Tanner staging

Male patients - Development of external genitalia

Stage 1: Pre-adolescent. Testes, scrotum, and penis are of about the same size and proportion as in early childhood.

Stage 2: The scrotum and testes have enlarged and there is a change in the texture of the scrotal skin.

Stage 3: Growth of the penis has occurred, at first mainly in length; these has been further growth of testes and scrotum

Stage 4: Penis further enlarged in length and breadth with development of glans. Testes and scrotum further enlarged. There is also further darkening of the scrotal skin

Stage 5: Genitalia adult in size and shape

Female patients - Breast development

Stage 1: Pre-adolescent; elevation of papilla only.

Stage 2: Breast bud stage; elevation of breast and papilla as a small mound, enlargement of areola diameter.

Stage 3: Further enlargement of breast and areola, with no separation of their contours.

Stage 4: Projection of areola and papilla to form a secondary mound above the level of the breast.

Stage 5: Mature stage; projection of papilla only, due to recession of the areola to the general contour of the breast.

The girls will be asked at each visit if they had begun to menstruate.

Male and female patients - Pubic hair

Stage 1: Pre-adolescent (can see velus hair similar to abdominal wall).

Stage 2: Sparse growth of long, slightly pigmented, downy hair, straight or only slightly curled, appearing chiefly along the labia or the base of the penis.

Stage 3: Considerably darker, coarser and more curled hair. The hair spreads sparsely over the junction of the pubes.

Stage 4: Hair is now adult in type, but the area covered by is still considerably smaller than in most adults. There is no spread to the medial surface of thighs.

Stage 5: Adult in quantity and type, distributed as an inverse triangle of the classically feminine pattern. Spread to the medial surface of the thighs (about age 15 years).

(Marshall and Tanner 1970; Marshall and Tanner 1969)

15 Appendix 3: Amount of blood to-be Drawn

Period	**Screen**	**Treatment**						
Visit	**1**	**2**	**3**	**4[T]**	**5**	**6**	**7[T]**	**8 and TD and/or PSW**
Day	**-28**	**1**	**10**	**90**	**180**	**190**	**270**	**365**
Week	**-4**			**12**	**26**		**39**	**52**
Central Laboratory - All Patients								
Hematology	3 mL				3 mL			3 mL
Chemistry	3.5 mL [6 mL (Australia only)]				3.5 mL			3.5 mL [6 mL (Australia only)]
Renal & Ca monitoring[1]			3.5 mL			3.5 mL		
Serum pregnancy[2]	2.5mL							2.5mL
Specialized serum bone-markers		3 mL			3 mL			3 mL
Vitamin D	2.5 mL							2.5 mL
Local Laboratory - All Patients								
Serum creatinine	2.5 mL	2.5 mL						
Serum ionized calcium		2.5 mL						
TOTALS	**14 mL [16.5mL (Australia only)]**	**8 mL**	**3.5mL**	**-**	**9.5mL**	**3.5mL**	**-**	**14.5 mL [17.0mL (Australia only)]**

[1]Serum creatinine, urea, electrolytes, calcium, magnesium, phosphorus only
[2]Only in girls of child bearing potential

16 Appendix 4: Faces Pain Scale – Revised

Faces Pain Scale – Revised (FPS-R)

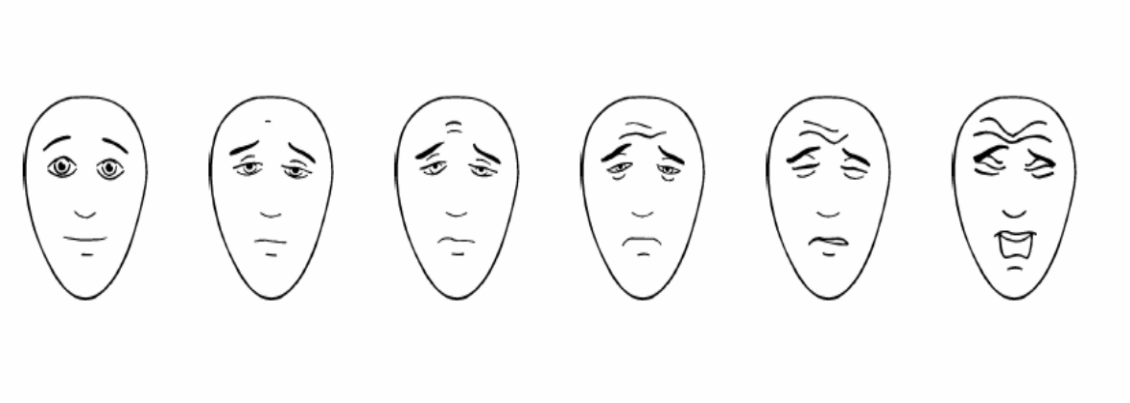
From *Pediatric Pain Sourcebook*, **www.painsourcebook.ca**
Version: 7 Aug 2007 CL von Baeyer

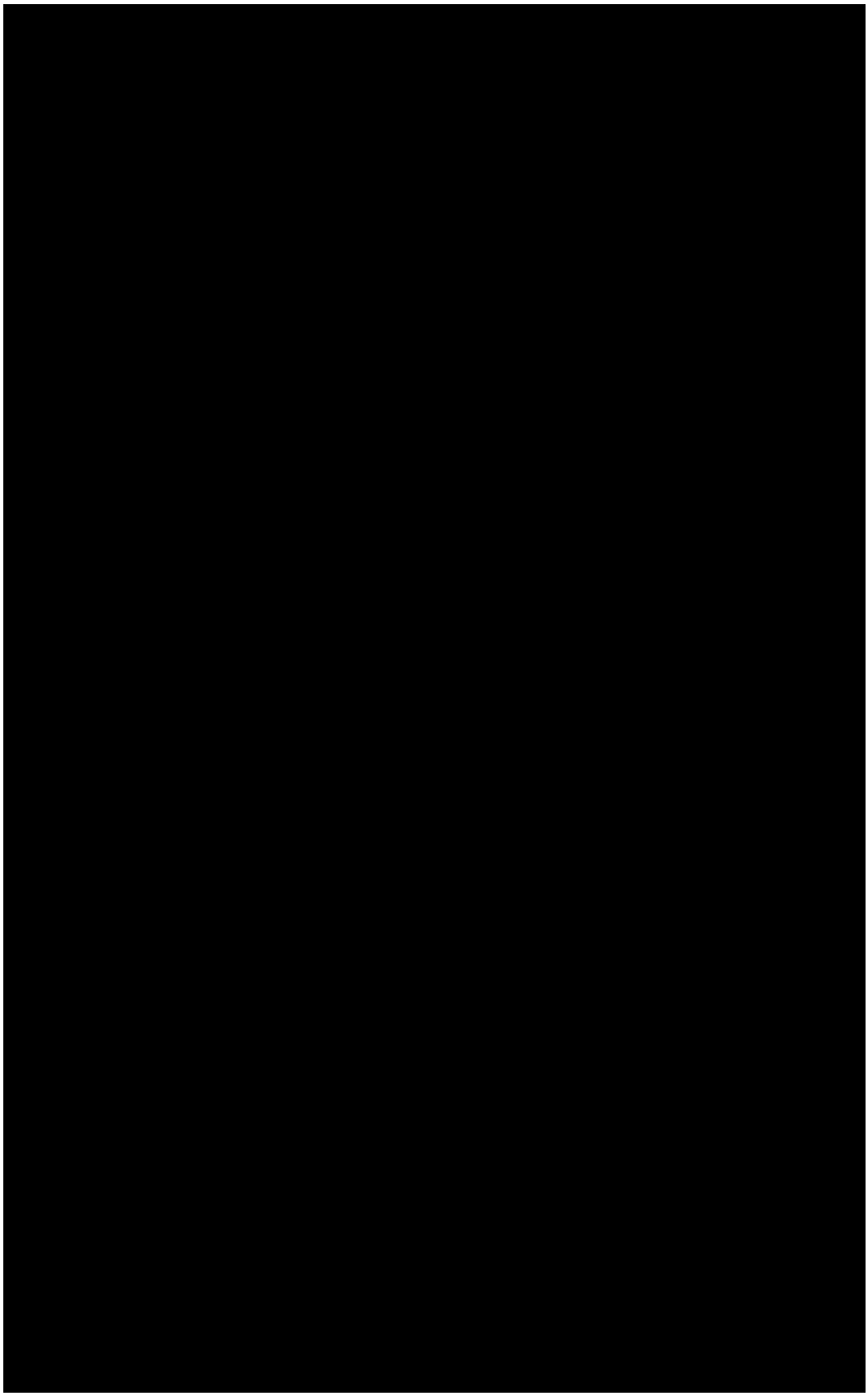
In the following instructions, say "hurt" or "pain," whichever seems right for a particular child.

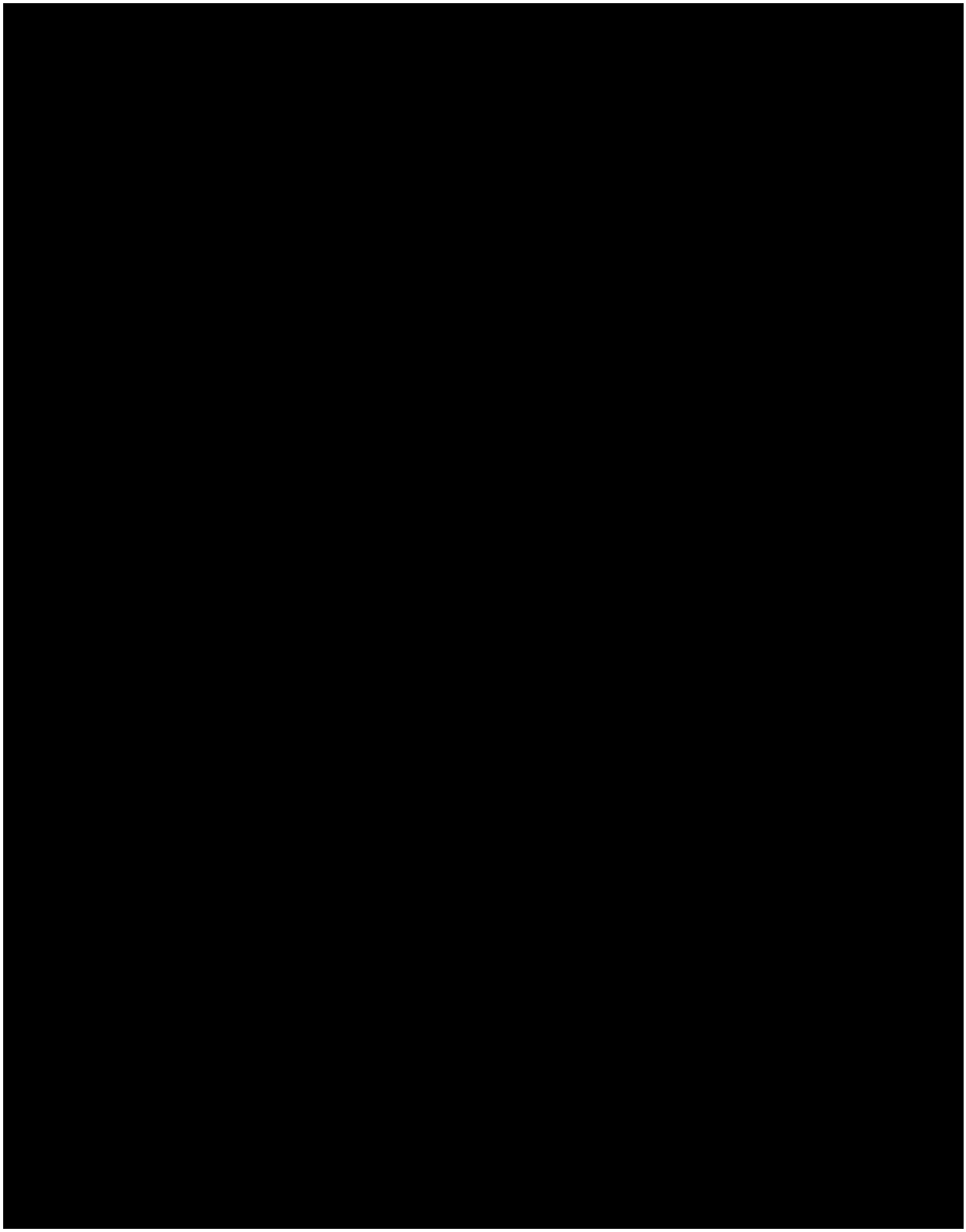
"These faces show how much something can hurt. This face *[point to left-most face]* **shows no pain. The faces show more and more pain** *[point to each from left to right]* **up to this one** *[point to right-most face]* **– it shows very much pain. Point to the face that shows how much you hurt** [right now]**."**

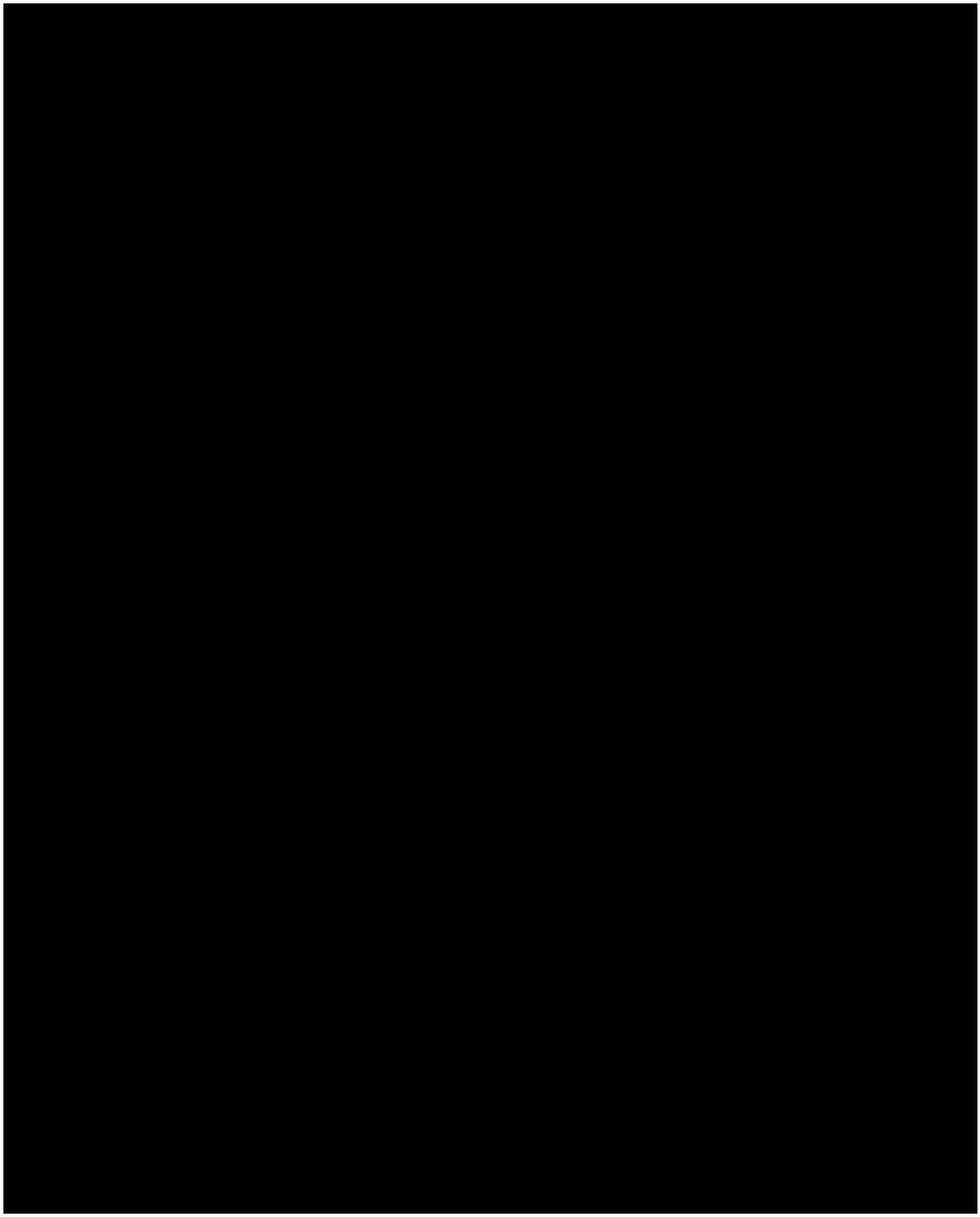
Score the chosen face 0, 2, 4, 6, 8, or 10, counting left to right, so '0' = 'no pain' and '10' = 'very much pain.' Do not use words like 'happy' and 'sad'. This scale is intended to measure how children feel inside, not how their face looks.

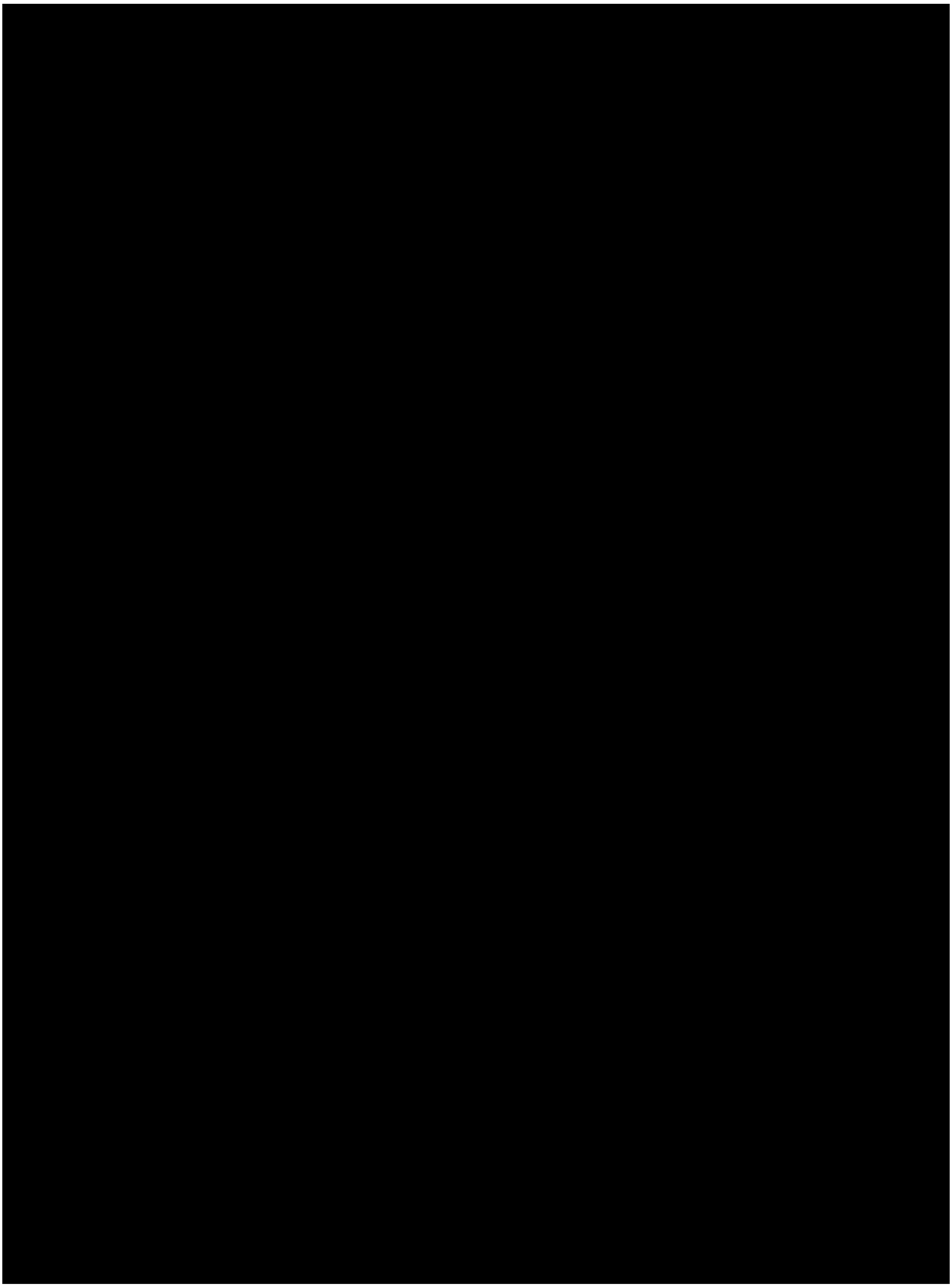
0 2 4 6 8 10

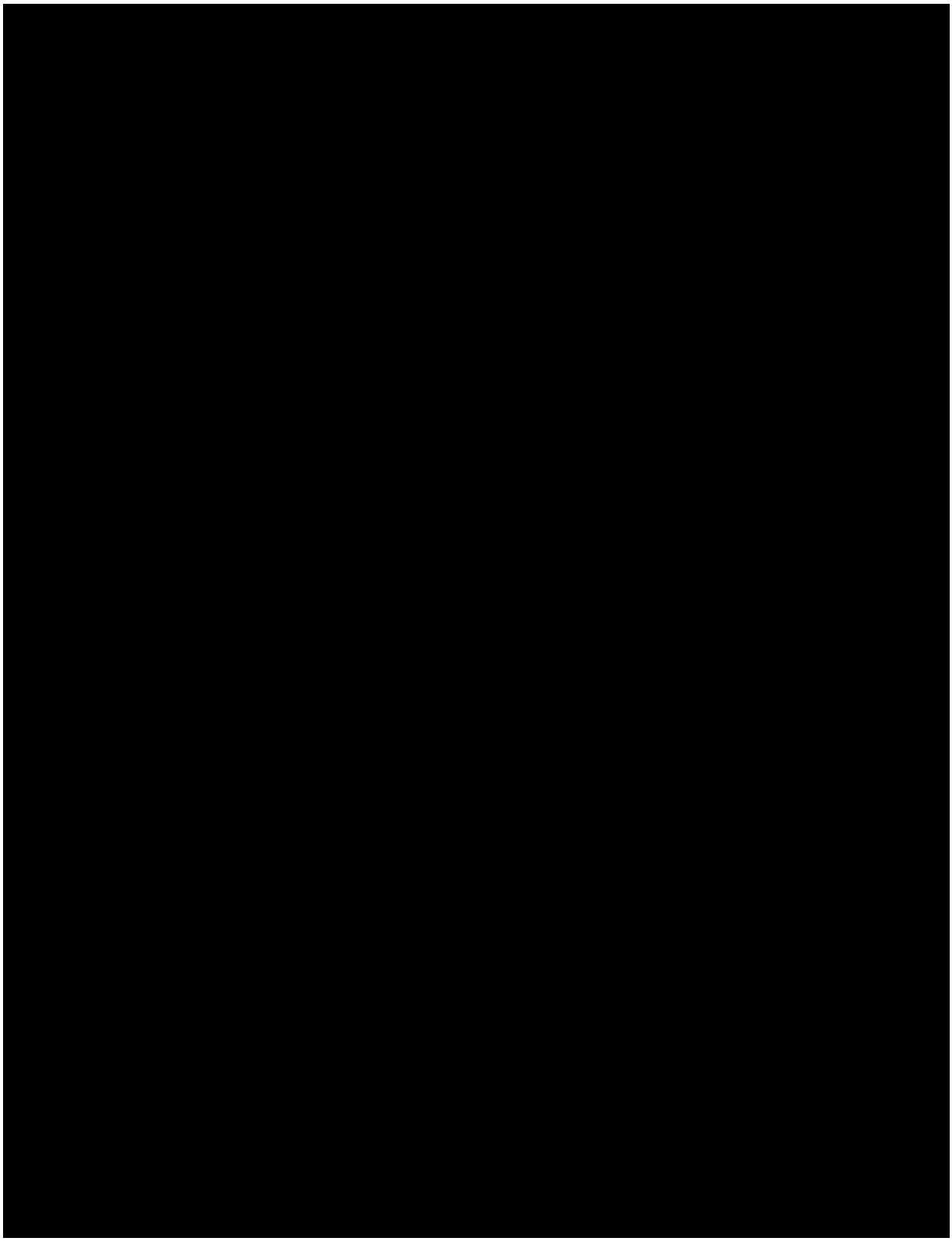












19 Appendix 7: Other subtypes of Osteoporosis in Children

Allowed	Disallowed
Cerebral palsy	Leukemia
Becker's dystrophy	Solid tumors
Diabetes mellitus	Thalassemia
Celiac disease	Mastocytosis
Cystic fibrosis	Hypogonadism
	Growth Hormone deficiency
	Hyperthyroidism
	Vitamin D deficiency
	Anorexia nervosa
	Chronic kidney disease
	Secondary hyperparathyroidism
	Organ transplant recipient
	Biliary atresia
	Female athletic triad
	Spinal cord injury